Essential Etheric Oils

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Contents

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References

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Cannabinoid

Cannabinoids are a class of diverse chemical compounds that activate cannabinoid receptors on cells that repress neurotransmitter release in the brain. These receptor proteins include the endocannabinoids (produced naturally in the body by humans and animals),[] the phytocannabinoids (found in cannabis and some other plants), and synthetic cannabinoids (produced chemically by humans). The most notable cannabinoid is the phytocannabinoid Δ^9-tetrahydrocannabinol (THC), the primary psychoactive compound of cannabis.[][1] Cannabidiol (CBD) is another major constituent of the plant, representing up to 40% in its extracts.[2] There are at least 85 different cannabinoids isolated from cannabis, exhibiting varied effects.[3]

Synthetic cannabinoids encompass a variety of distinct chemical classes: the classical cannabinoids structurally related to THC, the nonclassical cannabinoids (cannabimimetics) including the aminoalkylindoles, 1,5-diarylpyrazoles, quinolines, and arylsulphonamides, as well as eicosanoids related to the endocannabinoids.[]

Cannabinoid receptors

Before the 1980s, it was often speculated that cannabinoids produced their physiological and behavioral effects via nonspecific interaction with cell membranes, instead of interacting with specific membrane-bound receptors. The discovery of the first cannabinoid receptors in the 1980s helped to resolve this debate. These receptors are common in animals, and have been found in mammals, birds, fish, and reptiles. At present, there are two known types of cannabinoid receptors, termed CB_1 and CB_2,[] with mounting evidence of more.[] The human brain has more cannabinoid receptors than any other G protein-coupled receptor (GPCR) type.[]

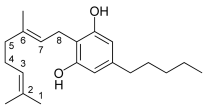
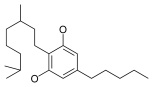
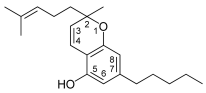
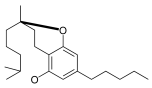
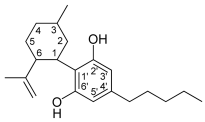
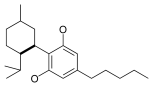
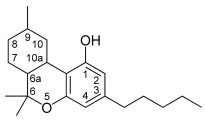
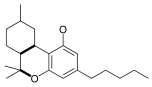
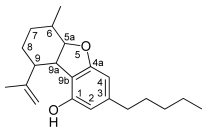
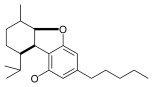
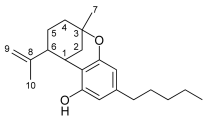
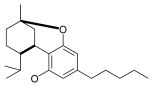
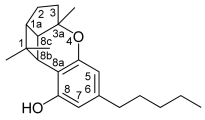
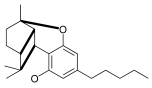
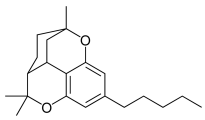
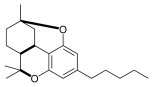
Cannabinoid receptor type 1

CB_1 receptors are found primarily in the brain, to be specific in the basal ganglia and in the limbic system, including the hippocampus.[] They are also found in the cerebellum and in both male and female reproductive systems. CB_1 receptors are absent in the medulla oblongata, the part of the brain stem responsible for respiratory and cardiovascular functions. Thus, there is not the risk of respiratory or cardiovascular failure that can be produced by some drugs. CB_1 receptors appear to be responsible for the euphoric and anticonvulsive effects of cannabis.

Cannabinoid receptor type 2

CB_2 receptors are predominantly found in the immune system, or immune-derived cells[] with the greatest density in the spleen. While found only in the peripheral nervous system, a report does indicate that CB_2 is expressed by a subpopulation of microglia in the human cerebellum .[] CB_2 receptors appear to be responsible for the anti-inflammatory and possibly other therapeutic effects of cannabis.[]

Phytocannabinoids

Type	Skeleton	Cyclization
Cannabigerol-type **CBG**		
Cannabichromene-type **CBC**		
Cannabidiol-type **CBD**		
Tetrahydrocannabinol- and Cannabinol-type **THC, CBN**		
Cannabielsoin-type **CBE**		
iso-Tetrahydrocannabinol-type ***iso*-THC**		
Cannabicyclol-type **CBL**		
Cannabicitran-type **CBT**		
Main classes of natural cannabinoids		

The bud of a Cannabis sativa flower coated with THC-laden trichomes

Phytocannabinoids (also called *natural cannabinoids*, *herbal cannabinoids*, and *classical cannabinoids*) are known to occur in several different plant species. These include *Cannabis sativa*, *Cannabis indica*, *Cannabis ruderalis*, *Echinacea purpurea*, *Echinacea angustifolia*, *Echinacea pallida*, *Acmella oleracea*, *Helichrysum umbraculigerum*, and *Radula marginata*.[] The best known herbal cannabinoids are Δ9-tetrahydrocannabinol (THC) from *Cannabis* and the lipophilic alkamides (alkylamides) from *Echinacea* species.[]

At least 85 different cannabinoids have been isolated from the Cannabis plant[4] and 25 different cannabinoids from Echinacea species.[] In *Cannabis*, these cannabinoids are concentrated in a viscous resin produced in structures known as glandular trichomes. In *Echinacea* species, cannabinoids are found throughout the plant structure, but are most concentrated in the roots and stems.[] Tea (Camellia sinensis) catechins have an affinity for human cannabinoid receptors.[]

Phytocannabinoids are nearly insoluble in water but are soluble in lipids, alcohols, and other non-polar organic solvents. However, as phenols, they form more water-soluble phenolate salts under strongly alkaline conditions.

All-natural cannabinoids are derived from their respective 2-carboxylic acids (2-COOH) by decarboxylation (catalyzed by heat, light, or alkaline conditions).

Cannabis indica plant

Cannabis-derived cannabinoids

Types

To the right, the main classes of cannabinoids from *Cannabis* are shown. All classes derive from cannabigerol-type compounds and differ mainly in the way this precursor is cyclized.

Tetrahydrocannabinol (THC), cannabidiol (CBD), cannabinol (CBN) (derived from *Cannabis*); and dodeca-2E,4E,8Z,10E/Z-tetraenoic-acid-isobutylamides (the main bioactive constituents from *Echinacea* species) are the most prevalent natural cannabinoids and have received the most study.

- CBG (Cannabigerol)
- CBC (Cannabichromene)
- CBL (Cannabicyclol)
- CBV (Cannabivarin)
- THCV (Tetrahydrocannabivarin)
- CBDV (Cannabidivarin)
- CBCV (Cannabichromevarin)
- CBGV (Cannabigerovarin)
- CBGM (Cannabigerol Monomethyl Ether)

Tetrahydrocannabinol

Tetrahydrocannabinol (THC) is the primary psychoactive component of the Cannabis plant. *Delta*-9-tetrahydrocannabinol (Δ^9-THC, THC) and *delta*-8-tetrahydrocannabinol (Δ^8-THC), mimic the action of anandamide, a neurotransmitter produced naturally in the body. These two THC's produce the effects associated with cannabis by binding to the CB_1 cannabinoid receptors in the brain. THC appears to ease moderate pain (analgesic) and to be neuroprotective. Studies show THC reduces neuroinflammation and stimulates neurogenesis.[5][6][7] THC has approximately equal affinity for the CB_1 and CB_2 receptors.[8]

Cannabidiol

Cannabidiol (CBD) is not psychoactive, and was thought not to affect the psychoactivity of THC.[] However, recent evidence shows that smokers of cannabis with a higher CBD/THC ratio were less likely to experience schizophrenia-like symptoms.[] This is supported by psychological tests, in which participants experience less intense psychotic-like effects when intravenous THC was co-administered with CBD (as measured with a PANSS test).[] Cannabidiol has little affinity for CB_1 and CB_2 receptors but acts as an indirect antagonist of cannabinoid agonists.[] Recently it was found to be an antagonist at the putative new cannabinoid receptor, GPR55, a GPCR expressed in the caudate nucleus and putamen.[9] Cannabidiol has also been shown to act as a 5-HT_{1A} receptor agonist,[] an action that is involved in its antidepressant,[][] anxiolytic,[][] and neuroprotective[][] effects.

It appears to relieve convulsion, inflammation, anxiety, and nausea.[] CBD has a greater affinity for the CB_2 receptor than for the CB_1 receptor.[]

CBD shares a precursor with THC and is the main cannabinoid in low-THC *Cannabis* strains. CBD apparently plays a role in preventing the short-term memory loss associated with THC in mammals.

Some research suggests that the antipsychotic effects of cannabidiol potentially represent a novel mechanism in the treatment of schizophrenia.[10]

Researchers at California Pacific Medical Center discovered CBD's ability to "turn off" the activity of ID1, the gene responsible for metastasis in breast and other types of cancers, including the particularly aggressive triple negative breast cancer.[11][12][13] The researchers hope to start human trials soon.[14]

Cannabinol

Cannabinol (CBN) is the primary product of THC degradation, and there is usually little of it in a fresh plant. CBN content increases as THC degrades in storage, and with exposure to light and air. It is only mildly psychoactive. Its affinity to the CB_2 receptor is higher than for the CB_1 receptor.[]

Cannabigerol

Cannabigerol (CBG) is non-psychotomimetic but still affects the overall effects of Cannabis. It acts as an α_2-adrenergic receptor agonist, 5-HT_{1A} receptor antagonist, and CB_1 receptor antagonist.[] It also binds to the CB_2 receptor.[]

Tetrahydrocannabivarin

Tetrahydrocannabivarin (THCV) is prevalent in certain central Asian and southern African strains of *Cannabis*.[15][] It is an antagonist of THC at CB_1 receptors and attenuates the psychoactive effects of THC.[16]

Cannabidivarin

Although cannabidivarin (CBDV) is usually a minor constituent of the cannabinoid profile, enhanced levels of CBDV have been reported in feral cannabis plants from the northwest Himalayas, and in hashish from Nepal.[17][]

Cannabichromene

Cannabichromene (CBC) is non-psychoactive and does not affect the psychoactivity of THC .[]

Double bond position

In addition, each of the compounds above may be in different forms depending on the position of the double bond in the alicyclic carbon ring. There is potential for confusion because there are different numbering systems used to describe the position of this double bond. Under the dibenzopyran numbering system widely used today, the major form of THC is called Δ^9-THC, while the minor form is called Δ^8-THC. Under the alternate terpene numbering system, these same compounds are called Δ^1-THC and Δ^6-THC, respectively.

Length

Most herbal cannabinoid compounds are 21-carbon compounds. However, some do not follow this rule, primarily because of variation in the length of the side-chain attached to the aromatic ring. In THC, CBD, and CBN, this side-chain is a pentyl (5-carbon) chain. In the most common homologue, the pentyl chain is replaced with a propyl (3-carbon) chain. Cannabinoids with the propyl side-chain are named using the suffix *varin*, and are designated, for example, THCV, CBDV, or CBNV.

Cannabis plant profile

Cannabis plants can exhibit wide variation in the quantity and type of cannabinoids they produce. The mixture of cannabinoids produced by a plant is known as the plant's cannabinoid profile. Selective breeding has been used to control the genetics of plants and modify the cannabinoid profile. For example, strains that are used as fiber (commonly called hemp) are bred such that they are low in psychoactive chemicals like THC. Strains used in medicine are often bred for high CBD content, and strains used for recreational purposes are usually bred for high THC content or for a specific chemical balance.

Quantitative analysis of a plant's cannabinoid profile is often determined by gas chromatography (GC), or more reliably by gas chromatography combined with mass spectrometry (GC/MS). Liquid chromatography (LC) techniques are also possible, and, unlike GC methods, can differentiate between the acid and neutral forms of the cannabinoids. There have been systematic attempts to monitor the cannabinoid profile of cannabis over time, but their accuracy is impeded by the illegal status of the plant in many countries.

Pharmacology

Cannabinoids can be administered by smoking, vaporizing, oral ingestion, transdermal patch, intravenous injection, sublingual absorption, or rectal suppository. Once in the body, most cannabinoids are metabolized in the liver, especially by cytochrome P450 mixed-function oxidases, mainly CYP 2C9. Thus supplementing with CYP 2C9 inhibitors leads to extended intoxication.

Some is also stored in fat in addition to being metabolized in liver. Δ^9-THC is metabolized to 11-hydroxy-Δ^9-THC, which is then metabolized to 9-carboxy-THC. Some cannabis metabolites can be detected in the body several weeks after administration. These metabolites are the chemicals recognized by common antibody-based "drug tests"; in the case of THC et al., these loads do not represent intoxication (compare to ethanol breath tests that measure instantaneous blood alcohol levels) but an integration of past consumption over an approximately month-long window.

Plant synthesis

Cannabinoid production starts when an enzyme causes geranyl pyrophosphate and olivetolic acid to combine and form CBG. Next, CBG is independently converted to either CBD or CBC by two separate synthase enzymes. CBD is then enzymatically cyclized to THC. For the propyl homologues (THCV, CBDV and CBNV), there is a similar pathway that is based on CBGV. Recent studiesWikipedia:Avoid weasel words show that THC is not cyclized from CBD but rather directly from CBG. No experiment thus far has turned up an enzyme that converts CBD into THC, although it is still hypothesizedWikipedia:Avoid weasel words.

Separation

Cannabinoids can be separated from the plant by extraction with organic solvents. Hydrocarbons and alcohols are often used as solvents. However, these solvents are flammable and many are toxic. Butane may be used, which evaporates extremely quickly. Supercritical solvent extraction with carbon dioxide is an alternative technique. Although this process requires high pressures (73 atmospheres or more), there is minimal risk of fire or toxicity, solvent removal is simple and efficient, and extract quality can be well controlled. Once extracted, cannabinoid blends can be separated into individual components using wiped film vacuum distillation or other distillation techniques. However, to produce high-purity cannabinoids, chemical synthesis or semisynthesis is generally required.

Natural occurrence

Cannabis indica may have a CBD:THC ratio 4–5 times that of *Cannabis sativa*.

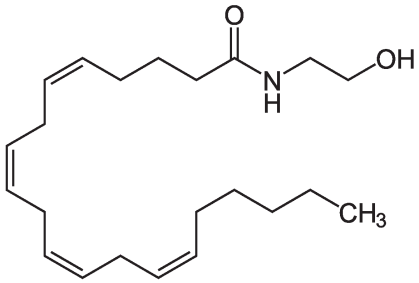
History

Cannabinoids were first discovered in the 1940s, when CBD and CBN were identified. The structure of THC was first determined in 1964.

Due to molecular similarity and ease of synthetic conversion, CBD was originally believed to be a natural precursor to THC. However, it is now known that CBD and THC are produced independently in the cannabis plant from the precursor CBG.

Endocannabinoids

Endocannabinoids are substances produced from within the body that activate cannabinoid receptors. After the discovery of the first cannabinoid receptor in 1988, scientists began searching for an endogenous ligand for the receptor.



Anandamide, an endogenous ligand of CB_1 and CB_2

Types of endocannabinoid ligands

Arachidonoylethanolamine (Anandamide or AEA)

In 1992, in Raphael Mechoulam's lab, the first such compound was identified as arachidonoyl ethanolamine and named anandamide, a name derived from the Sanskrit word for bliss and *-amide*. Anandamide is derived from the essential fatty acid arachidonic acid. It has a pharmacology similar to THC, although its chemical structure is different. Anandamide binds to the central (CB_1) and, to a lesser extent, peripheral (CB_2) cannabinoid receptors, where it acts as a partial agonist. Anandamide is about as potent as THC at the CB_1 receptor.[] Anandamide is found in nearly all tissues in a wide range of animals.[] Anandamide has also been found in plants, including small amounts in chocolate.[]

Two analogs of anandamide, 7,10,13,16-docosatetraenoylethanolamide and *homo*-γ-linolenoylethanolamine, have similar pharmacology. All of these are members of a family of signalling lipids called *N*-acylethanolamines, which also includes the noncannabimimetic palmitoylethanolamide and oleoylethanolamide, which possess anti-inflammatory and orexigenic effects, respectively. Many *N*-acylethanolamines have also been identified in plant seeds[18] and in molluscs.[19]

2-arachidonoyl glycerol (2-AG)

Another endocannabinoid, 2-arachidonoyl glycerol, binds to both the CB_1 and CB_2 receptors with similar affinity, acting as a full agonist at both.[] 2-AG is present at significantly higher concentrations in the brain than anandamide,[] and there is some controversy over whether 2-AG rather than anandamide is chiefly responsible for endocannabinoid signalling *in vivo*.[] In particular, one *in vitro* study suggests that 2-AG is capable of stimulating higher G-protein activation than anandamide, although the physiological implications of this finding are not yet known.[20]

2-arachidonyl glyceryl ether (noladin ether)

In 2001, a third, ether-type endocannabinoid, 2-arachidonyl glyceryl ether (noladin ether), was isolated from porcine brain.[21] Prior to this discovery, it had been synthesized as a stable analog of 2-AG; indeed, some controversy remains over its classification as an endocannabinoid, as another group failed to detect the substance at "any appreciable amount" in the brains of several different mammalian species.[] It binds to the CB_1 cannabinoid receptor (K_i = 21.2 nmol/L) and causes sedation, hypothermia, intestinal immobility, and mild antinociception in mice. It binds primarily to the CB_1 receptor, and only weakly to the CB_2 receptor.[]

N-arachidonoyl-dopamine (NADA)

Discovered in 2000, NADA preferentially binds to the CB_1 receptor.[22] Like anandamide, NADA is also an agonist for the vanilloid receptor subtype 1 (TRPV1), a member of the vanilloid receptor family.[][23]

Virodhamine (OAE)

A fifth endocannabinoid, virodhamine, or *O*-arachidonoyl-ethanolamine (OAE), was discovered in June 2002. Although it is a full agonist at CB_2 and a partial agonist at CB_1, it behaves as a CB_1 antagonist *in vivo*. In rats, virodhamine was found to be present at comparable or slightly lower concentrations than anandamide in the brain, but 2- to 9-fold higher concentrations peripherally.[24]

Lysophosphatidylinositol (LPI)

Recent evidence has highlighted LPI as the endogenous ligand to novel endocannabinoid receptor GPR55, making it a strong contender as the sixth endocannabinoid. [25]

Function

Endocannabinoids serve as intercellular 'lipid messengers', signaling molecules that are released from one cell and activating the cannabinoid receptors present on other nearby cells. Although in this intercellular signaling role they are similar to the well-known monoamine neurotransmitters, such as acetylcholine and dopamine, endocannabinoids differ in numerous ways from them. For instance, they are used in retrograde signaling between neurons. Furthermore, endocannabinoids are lipophilic molecules that are not very soluble in water. They are not stored in vesicles, and exist as integral constituents of the membrane bilayers that make up cells. They are believed to be synthesized 'on-demand' rather than made and stored for later use. The mechanisms and enzymes underlying the biosynthesis of endocannabinoids remain elusive and continue to be an area of active research.

The endocannabinoid 2-AG has been found in bovine and human maternal milk.[26]

Retrograde signal

Conventional neurotransmitters are released from a ‘presynaptic’ cell and activate appropriate receptors on a ‘postsynaptic’ cell, where presynaptic and postsynaptic designate the sending and receiving sides of a synapse, respectively. Endocannabinoids, on the other hand, are described as retrograde transmitters because they most commonly travel ‘backward’ against the usual synaptic transmitter flow. They are, in effect, released from the postsynaptic cell and act on the presynaptic cell, where the target receptors are densely concentrated on axonal terminals in the zones from which conventional neurotransmitters are released. Activation of cannabinoid receptors temporarily reduces the amount of conventional neurotransmitter released. This endocannabinoid mediated system permits the postsynaptic cell to control its own incoming synaptic traffic. The ultimate effect on the endocannabinoid-releasing cell depends on the nature of the conventional transmitter being controlled. For instance, when the release of the inhibitory transmitter GABA is reduced, the net effect is an increase in the excitability of the endocannabinoid-releasing cell. On the converse, when release of the excitatory neurotransmitter glutamate is reduced, the net effect is a decrease in the excitability of the endocannabinoid-releasing cell.

Range

Endocannabinoids are hydrophobic molecules. They cannot travel unaided for long distances in the aqueous medium surrounding the cells from which they are released, and therefore act locally on nearby target cells. Hence, although emanating diffusely from their source cells, they have much more restricted spheres of influence than do hormones, which can affect cells throughout the body.

Synthetic cannabinoids

Historically, laboratory synthesis of cannabinoids were often based on the structure of herbal cannabinoids, and a large number of analogs have been produced and tested, especially in a group led by Roger Adams as early as 1941 and later in a group led by Raphael Mechoulam. Newer compounds are no longer related to natural cannabinoids or are based on the structure of the endogenous cannabinoids.

Synthetic cannabinoids are particularly useful in experiments to determine the relationship between the structure and activity of cannabinoid compounds, by making systematic, incremental modifications of cannabinoid molecules.

Medications containing natural or synthetic cannabinoids or cannabinoid analogs:

- Dronabinol (Marinol), is Δ^9-tetrahydrocannabinol (THC), used as an appetite stimulant, anti-emetic, and analgesic
- Nabilone (Cesamet), a synthetic cannabinoid and an analog of Marinol. It is Schedule II unlike Marinol, which is Schedule III
- Sativex, a cannabinoid extract oral spray containing THC, CBD, and other cannabinoids used for neuropathic pain and spasticity in 22 countries including England, Canada and Spain. Sativex develops whole-plant cannabinoid medicines
- Rimonabant (SR141716), a selective cannabinoid (CB_1) receptor inverse agonist once used as an anti-obesity drug under the proprietary name Acomplia. It was also used for smoking cessation

Other notable Wikipedia:Please clarify synthetic cannabinoids include:

- JWH-018, a potent synthetic cannabinoid agonist discovered by Dr. John W. Huffman at Clemson University. It is being increasingly sold in legal smoke blends collectively known as "spice". Several countries and states have moved to ban it legally.
- JWH-073
- CP-55940, produced in 1974, this synthetic cannabinoid receptor agonist is many times more potent than THC.
- Dimethylheptylpyran
- HU-210, about 100 times as potent as THC[27]
- HU-331 a potential anti-cancer drug derived from cannabidiol that specifically inhibits topoisomerase II.
- SR144528, a CB_2 receptor antagonist
- WIN 55,212-2, a potent cannabinoid receptor agonist
- JWH-133, a potent selective CB_2 receptor agonist
- Levonantradol (Nantrodolum), an anti-emetic and analgesic but not currently in use in medicine
- AM-2201, a potent cannabinoid receptor agonist.

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External links

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- Marijuana and Medicine - Assessing the Science Base (Institute of Medicine) - 1999 (http://books.nap.edu/html/marimed/) at National Academies Press
- House of Lords Report - Cannabis (United Kingdom) - 1998 (http://www.parliament.the-stationery-office.co.uk/pa/ld199798/ldselect/ldsctech/151/15101.htm) at Parliament of the United Kingdom
- Cannabis: A Health Perspective and Research Agenda - 1997 (http://whqlibdoc.who.int/hq/1997/WHO_MSA_PSA_97.4.pdf) at World Health Organization
- Chemical Ecology of Cannabis (J. Intl. Hemp Assn. - 1994) (http://www.hempfood.com/IHA/iha01201.html)
- THC (tetrahydrocannabinol) accumulation in glands of Cannabis (Cannabaceae) (http://www.hempreport.com/issues/17/malbody17.html)
- Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb (PDF) (http://www.onlinepot.org/medical/Izzo Plant Cannabinoids Therapeutic Opportunities TIPS 2009.pdf)

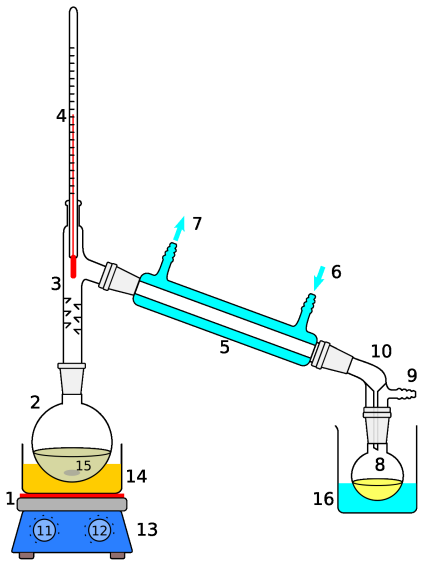
Cannabinoid research organizations

- The International Cannabinoid Research Society (http://www.cannabinoidsociety.org)
- The Canadian Consortium for the Investigation of Cannabinoids (http://www.ccic.net)
- Therapeutic Potential in Spotlight at Cannabinoid Researchers' Meeting (http://www.ccrmg.org/journal/04spr/potential.html) at California Cannabis Research Medical Group
- International Cannabinoid Research Society (http://cannabinoidsociety.org/)

Distillation

Distillation is a method of separating mixtures based on differences in volatility of components in a boiling liquid mixture. Distillation is a unit operation, or a physical separation process, and not a chemical reaction.

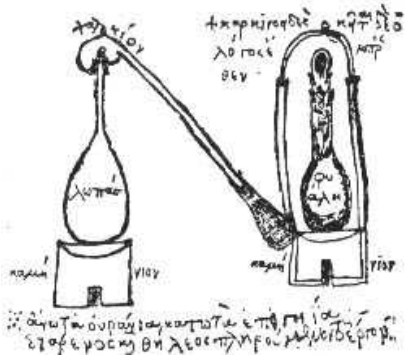
Commercially, distillation has a number of applications. It is used to separate crude oil into more fractions for specific uses such as transport, power generation and heating. Water is distilled to remove impurities, such as salt from seawater. Air is distilled to separate its components—notably oxygen, nitrogen, and argon— for industrial use. Distillation of fermented solutions has been used since ancient times to produce distilled beverages with a higher alcohol content. The premises where distillation is carried out, especially distillation of alcohol, are known as a **distillery**. A **still** is the apparatus used for distillation.



Laboratory display of distillation: **1:** A heating device **2:** Still pot **3:** Still head **4:** Thermometer/Boiling point temperature **5:** Condenser **6:** Cooling water in **7:** Cooling water out **8:** Distillate/receiving flask **9:** Vacuum/gas inlet **10:** Still receiver **11:** Heat control **12:** Stirrer speed control **13:** Stirrer/heat plate **14:** Heating (Oil/sand) bath **15:** Stirring means e.g.(shown), boiling chips or mechanical stirrer **16:** Cooling bath.[]

History

The first clear evidence of distillation comes from Greek alchemists working in Alexandria in the 1st century AD.[] Distilled water has been known since at least c. 200, when Alexander of Aphrodisias described the process.[] Distillation in China could have begun during the Eastern Han Dynasty (1st–2nd centuries), but archaeological evidence indicates that actual distillation of beverages began in the Jin and Southern Song dynasties.[] A still was found in an archaeological site in Qinglong, Hebei province dating to the 12th century. Distilled beverages were more common during the Yuan dynasty.[] Arabs learned the process from the Egyptians and used it extensively in their chemical experiments[*citation needed*].



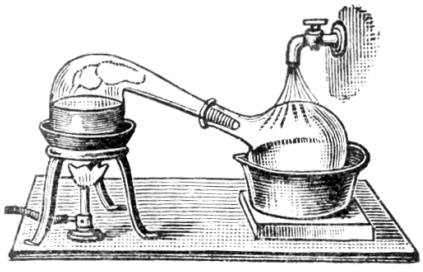
Distillation apparatus of Zosimos of Panopolis, from Marcelin Berthelot, *Collection des anciens alchimistes grecs* (3 vol., Paris, 1887–1888).

Clear evidence of the distillation of alcohol comes from the School of Salerno in the 12th century.[][1] Fractional distillation was developed by Tadeo Alderotti in the 13th century.[2]

In 1500, German alchemist Hieronymus Braunschweig published *Liber de arte destillandi* (The Book of the Art of Distillation)[3] the first book solely dedicated to the subject of distillation, followed in 1512 by a much expanded version. In 1651, John French published The Art of Distillation [4] the first major English compendium of practice, though it has been claimed[5] that much of it derives from Braunschweig's work. This includes diagrams with people in them showing the industrial rather than bench scale of the operation.

As alchemy evolved into the science of chemistry, vessels called retorts became used for distillations. Both alembics and retorts are forms of glassware with long necks pointing to the side at a downward angle which acted as air-cooled condensers to condense the distillate and let it drip downward for collection. Later, copper alembics were invented. Riveted joints were often kept tight by using various mixtures, for instance a dough made of rye flour.[6] These alembics often featured a cooling system around the beak, using cold water for instance, which made the condensation of alcohol more efficient. These were called pot stills. Today, the retorts and pot stills have been largely supplanted by more efficient distillation methods in most industrial processes. However, the pot still is still widely used for the elaboration of some fine alcohols such as cognac, Scotch whisky, tequila and some vodkas. Pot stills made of various materials (wood, clay, stainless steel) are also used by bootleggers in various countries. Small pot stills are also sold for the domestic production[7] of flower water or essential oils.

A retort



Distillation

Early forms of distillation were batch processes using one vaporization and one condensation. Purity was improved by further distillation of the condensate. Greater volumes were processed by simply repeating the distillation. Chemists were reported to carry out as many as 500 to 600 distillations in order to obtain a pure compound.[8]

In the early 19th century the basics of modern techniques including pre-heating and reflux were developed, particularly by the French,[8] then in 1830 a British Patent was issued to Aeneas Coffey for a whiskey distillation column,[9] which worked continuously and may be regarded as the archetype of modern petrochemical units. In 1877, Ernest Solvay was granted a U.S. Patent for a tray column for ammonia distillation[10] and the same and subsequent years saw developments of this theme for oil and spirits.

With the emergence of chemical engineering as a discipline at the end of the 19th century, scientific rather than empirical methods could be applied. The developing petroleum industry in the early 20th century provided the impetus for the development of accurate design methods such as the McCabe-Thiele method and the Fenske equation. The availability of powerful computers has also allowed direct computer simulation of distillation columns.

Old Ukrainian vodka still

Simple liqueur distillation in East Timor

Applications of distillation

The application of distillation can roughly be divided in four groups: laboratory scale, industrial distillation, distillation of herbs for perfumery and medicinals (herbal distillate), and food processing. The latter two are distinctively different from the former two in that in the processing of beverages, the distillation is not used as a true purification method but more to transfer all volatiles from the source materials to the distillate.

The main difference between laboratory scale distillation and industrial distillation is that laboratory scale distillation is often performed batch-wise, whereas industrial distillation often occurs continuously. In batch distillation, the composition of the source material, the vapors of the distilling compounds and the distillate change during the distillation. In batch distillation, a still is charged (supplied) with a batch of feed mixture, which is then separated into its component fractions which are collected sequentially from most volatile to less volatile, with the bottoms (remaining least or non-volatile fraction) removed at the end. The still can then be recharged and the process repeated.

In continuous distillation, the source materials, vapors, and distillate are kept at a constant composition by carefully replenishing the source material and removing fractions from both vapor and liquid in the system. This results in a better control of the separation process.

Idealized distillation model

The boiling point of a liquid is the temperature at which the vapor pressure of the liquid equals the pressure in the liquid, enabling bubbles to form without being crushed. A special case is the normal boiling point, where the vapor pressure of the liquid equals the ambient atmospheric pressure.

It is a common misconception that in a liquid mixture at a given pressure, each component boils at the boiling point corresponding to the given pressure and the vapors of each component will collect separately and purely. This, however, does not occur even in an idealized system. Idealized models of distillation are essentially governed by Raoult's law and Dalton's law, and assume that vapor-liquid equilibria are attained.

Raoult's law assumes that a component contributes to the total vapor pressure of the mixture in proportion to its percentage of the mixture and its vapor pressure when pure, or succinctly: partial pressure equals mole fraction multiplied by vapor pressure when pure. If one component changes another component's vapor pressure, or if the

volatility of a component is dependent on its percentage in the mixture, the law will fail.

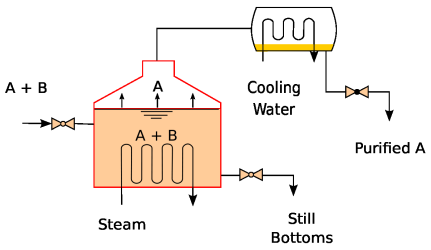
Dalton's law states that the total vapor pressure is the sum of the vapor pressures of each individual component in the mixture. When a multi-component liquid is heated, the vapor pressure of each component will rise, thus causing the total vapor pressure to rise. When the total vapor pressure reaches the pressure surrounding the liquid, boiling occurs and liquid turns to gas throughout the bulk of the liquid. Note that a mixture with a given composition has one boiling point at a given pressure, when the components are mutually soluble.

An implication of one boiling point is that lighter components never cleanly "boil first". At boiling point, all volatile components boil, but for a component, its percentage in the vapor is the same as its percentage of the total vapor pressure. Lighter components have a higher partial pressure and thus are concentrated in the vapor, but heavier volatile components also have a (smaller) partial pressure and necessarily evaporate also, albeit being less concentrated in the vapor. Indeed, batch distillation and fractionation succeed by varying the composition of the mixture. In batch distillation, the batch evaporates, which changes its composition; in fractionation, liquid higher in the fractionation column contains more lights and boils at lower temperatures.

The idealized model is accurate in the case of chemically similar liquids, such as benzene and toluene. In other cases, severe deviations from Raoult's law and Dalton's law are observed, most famously in the mixture of ethanol and water. These compounds, when heated together, form an azeotrope, which is a composition with a boiling point higher or lower than the boiling point of each separate liquid. Virtually all liquids, when mixed and heated, will display azeotropic behaviour. Although there are computational methods that can be used to estimate the behavior of a mixture of arbitrary components, the only way to obtain accurate vapor-liquid equilibrium data is by measurement.

It is not possible to *completely* purify a mixture of components by distillation, as this would require each component in the mixture to have a zero partial pressure. If ultra-pure products are the goal, then further chemical separation must be applied. When a binary mixture is evaporated and the other component, e.g. a salt, has zero partial pressure for practical purposes, the process is simpler and is called evaporation in engineering.

Batch distillation



A batch still showing the separation of A and B.

Heating an ideal mixture of two volatile substances A and B (with A having the higher volatility, or lower boiling point) in a batch distillation setup (such as in an apparatus depicted in the opening figure) until the mixture is boiling results in a vapor above the liquid which contains a mixture of A and B. The ratio between A and B in the vapor will be different from the ratio in the liquid: the ratio in the liquid will be determined by how the original mixture was prepared, while the ratio in the vapor will be enriched in the more volatile compound, A (due to Raoult's Law, see above). The vapor goes through the condenser and is removed from the system. This in turn means that the ratio of compounds in the remaining liquid is now different from the initial ratio (i.e. more enriched in B than the starting liquid).

The result is that the ratio in the liquid mixture is changing, becoming richer in component B. This causes the boiling point of the mixture to rise, which in turn results in a rise in the temperature in the vapor, which results in a changing ratio of A : B in the gas phase (as distillation continues, there is an increasing proportion of B in the gas phase). This results in a slowly changing ratio A : B in the distillate.

If the difference in vapor pressure between the two components A and B is large (generally expressed as the difference in boiling points), the mixture in the beginning of the distillation is highly enriched in component A, and when component A has distilled off, the boiling liquid is enriched in component B.

Continuous distillation

Continuous distillation is an ongoing distillation in which a liquid mixture is continuously (without interruption) fed into the process and separated fractions are removed continuously as output streams as time passes during the operation. Continuous distillation produces at least two output fractions, including at least one volatile distillate fraction, which has boiled and been separately captured as a vapor condensed to a liquid. There is always a bottoms (or residue) fraction, which is the least volatile residue that has not been separately captured as a condensed vapor.

Continuous distillation differs from batch distillation in the respect that concentrations should not change over time. Continuous distillation can be run at a steady state for an arbitrary amount of time. For any source material of specific composition, the main variables that affect the purity of products in continuous distillation are the reflux ratio and the number of theoretical equilibrium stages (practically, the number of trays or the height of packing). Reflux is a flow from the condenser back to the column, which generates a recycle that allows a better separation with a given number of trays. Equilibrium stages are ideal steps where compositions achieve vapor-liquid equilibrium, repeating the separation process and allowing better separation given a reflux ratio. A column with a high reflux ratio may have fewer stages, but it refluxes a large amount of liquid, giving a wide column with a large holdup. Conversely, a column with a low reflux ratio must have a large number of stages, thus requiring a taller column.

General improvements

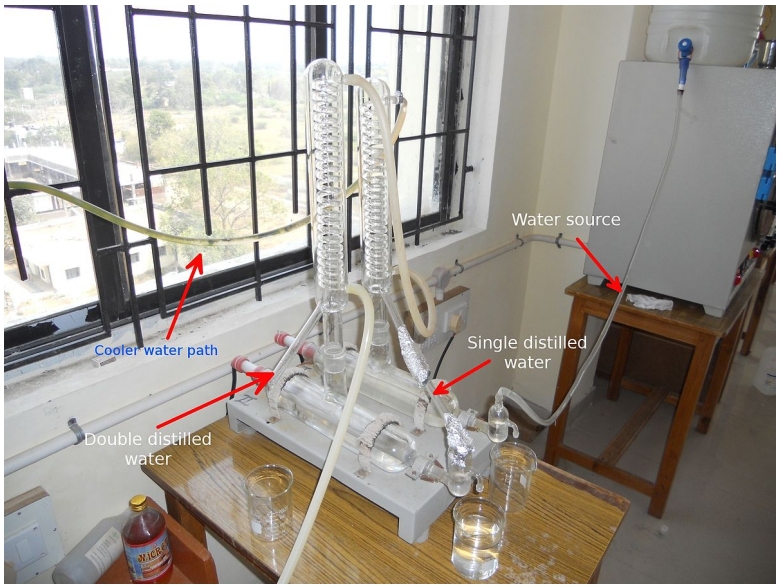
Both batch and continuous distillations can be improved by making use of a fractionating column on top of the distillation flask. The column improves separation by providing a larger surface area for the vapor and condensate to come into contact. This helps it remain at equilibrium for as long as possible. The column can even consist of small subsystems ('trays' or 'dishes') which all contain an enriched, boiling liquid mixture, all with their own vapor-liquid equilibrium.

There are differences between laboratory-scale and industrial-scale fractionating columns, but the principles are the same. Examples of laboratory-scale fractionating columns (in increasing efficiency) include:

- Air condenser
- Vigreux column (usually laboratory scale only)
- Packed column (packed with glass beads, metal pieces, or other chemically inert material)
- Spinning band distillation system.

Laboratory scale distillation

Laboratory scale distillations are almost exclusively run as batch distillations. The device used in distillation, sometimes referred to as a *still*, consists at a minimum of a **reboiler** or *pot* in which the source material is heated, a **condenser** in which the heated vapour is cooled back to the liquid state, and a **receiver** in which the concentrated or purified liquid, called the **distillate**, is collected. Several laboratory scale techniques for distillation exist (see also distillation types).



Typical laboratory distillation unit

Simple distillation

In **simple distillation**, the vapor is immediately channeled into a condenser. Consequently, the distillate is not pure but rather its composition is identical to the composition of the vapors at the given temperature and pressure. That concentration follows Raoult's law.

As a result, simple distillation is effective only when the liquid boiling points differ greatly (rule of thumb is 25 °C)[11] or when separating liquids from non-volatile solids or oils. For these cases, the vapor pressures of the components are usually sufficiently different that the distillate may be sufficiently pure for its intended purpose.

Fractional distillation

For many cases, the boiling points of the components in the mixture will be sufficiently close that Raoult's law must be taken into consideration. Therefore, **fractional distillation** must be used in order to separate the components by repeated vaporization-condensation cycles within a packed fractionating column. This separation, by successive distillations, is also referred to as **rectification**.[]

As the solution to be purified is heated, its vapors rise to the fractionating column. As it rises, it cools, condensing on the condenser walls and the surfaces of the packing material. Here, the condensate continues to be heated by the rising hot vapors; it vaporizes once more. However, the composition of the fresh vapors are determined once again by Raoult's law. Each vaporization-condensation cycle (called a *theoretical plate*) will yield a purer solution of the more volatile component.[12] In reality, each cycle at a given temperature does not occur at exactly the same position in the fractionating column; *theoretical plate* is thus a concept rather than an accurate description.

More theoretical plates lead to better separations. A spinning band distillation system uses a spinning band of Teflon or metal to force the rising vapors into close contact with the descending condensate, increasing the number of theoretical plates.[13]

Steam distillation

Like vacuum distillation, **steam distillation** is a method for distilling compounds which are heat-sensitive.[] The temperature of the steam is easier to control than the surface of a heating element, and allows a high rate of heat transfer without heating at a very high temperature. This process involves bubbling steam through a heated mixture of the raw material. By Raoult's law, some of the target compound will vaporize (in accordance with its partial pressure). The vapor mixture is cooled and condensed, usually yielding a layer of oil and a layer of water.

Steam distillation of various aromatic herbs and flowers can result in two products; an essential oil as well as a watery herbal distillate. The essential oils are often used in perfumery and aromatherapy while the watery distillates have many applications in aromatherapy, food processing and skin care.

Dimethyl sulfoxide usually boils at 189 °C. Under a vacuum, it distills off into the receiver at only 70 °C.

Vacuum distillation

Some compounds have very high boiling points. To boil such compounds, it is often better to lower the pressure at which such compounds are boiled instead of increasing the temperature. Once the pressure is lowered to the vapor pressure of the compound (at the given temperature), boiling and the rest of the distillation process can commence. This technique is referred to as **vacuum distillation** and it is commonly found in the laboratory in the form of the rotary evaporator.

This technique is also very useful for compounds which boil beyond their decomposition temperature at atmospheric pressure and which would therefore be decomposed by any attempt to boil them under atmospheric pressure.

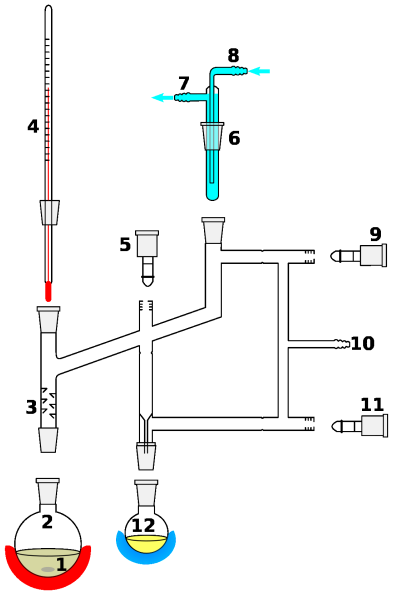
Molecular distillation is vacuum distillation below the pressure of 0.01 torr.[14] 0.01 torr is one order of magnitude above high vacuum, where fluids are in the free molecular flow regime, i.e. the mean free path of molecules is comparable to the size of the equipment. The gaseous phase no longer exerts significant pressure on the substance to be evaporated, and consequently, rate of evaporation no longer depends on pressure. That is, because the continuum assumptions of fluid dynamics no longer apply, mass transport is governed by molecular dynamics rather than fluid dynamics. Thus, a short path between the hot surface and the cold surface is necessary, typically by suspending a hot plate covered with a film of feed next to a cold plate with a line of sight in between. Molecular distillation is used industrially for purification of oils.

Air-sensitive vacuum distillation

Some compounds have high boiling points as well as being air sensitive. A simple vacuum distillation system as exemplified above can be used, whereby the vacuum is replaced with an inert gas after the distillation is complete. However, this is a less satisfactory system if one desires to collect fractions under a reduced pressure. To do this a

"cow" or "pig" adaptor can be added to the end of the condenser, or for better results or for very air sensitive compounds a Perkin triangle apparatus can be used.

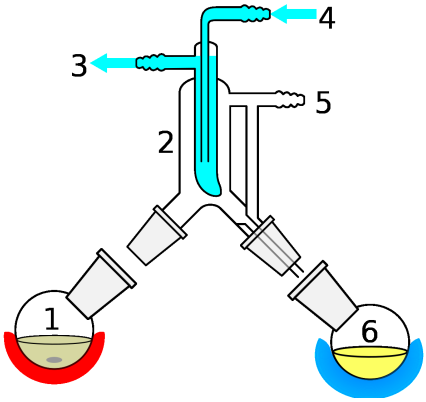
The Perkin triangle, has means via a series of glass or Teflon taps to allows fractions to be isolated from the rest of the still, without the main body of the distillation being removed from either the vacuum or heat source, and thus can remain in a state of reflux. To do this, the sample is first isolated from the vacuum by means of the taps, the vacuum over the sample is then replaced with an inert gas (such as nitrogen or argon) and can then be stoppered and removed. A fresh collection vessel can then be added to the system, evacuated and linked back into the distillation system via the taps to collect a second fraction, and so on, until all fractions have been collected.



Perkin triangle distillation setup
1: Stirrer bar/anti-bumping granules **2:** Still pot **3:** Fractionating column **4:** Thermometer/Boiling point temperature **5:** Teflon tap 1 **6:** Cold finger **7:** Cooling water out **8:** Cooling water in **9:** Teflon tap 2 **10:** Vacuum/gas inlet **11:** Teflon tap 3 **12:** Still receiver

Short path distillation

Short path distillation is a distillation technique that involves the distillate travelling a short distance, often only a few centimeters, and is normally done at reduced pressure.[] A classic example would be a distillation involving the distillate travelling from one glass bulb to another, without the need for a condenser separating the two chambers. This technique is often used for compounds which are unstable at high temperatures or to purify small amounts of compound. The advantage is that the heating temperature can be considerably lower (at reduced pressure) than the boiling point of the liquid at standard pressure, and the distillate only has to travel a short distance before condensing. A short path ensures that little compound is lost on the sides of the apparatus. The Kugelrohr is a kind of a short path distillation apparatus which often contain multiple chambers to collect distillate fractions.



Short path vacuum distillation apparatus with vertical condenser (cold finger), to minimize the distillation path; **1:** Still pot with stirrer bar/anti-bumping granules **2:** Cold finger – bent to direct condensate **3:** Cooling water out **4:** cooling water in **5:** Vacuum/gas inlet **6:** Distillate flask/distillate.

Zone distillation

Zone distillation is a distillation process in long container with partial melting of refined matter in moving liquid zone and condensation of vapor in the solid phase at condensate pulling in cold area. The process is worked in theory. When zone heater is moving from the top to the bottom of the container then solid condensate with irregular impurity distribution is forming. Then most pure part of the condensate may be extracted as product. The process may be iterated many

times by moving (without turnover) the received condensate to the bottom part of the container on the place of refined matter. The irregular impurity distribution in the condensate (that is efficiency of purification) increases with number of repetitions of the process. Zone distillation is a distillation analog of zone recrystallization. Impurity distribution in the condensate is described by known equations of zone recrystallization with various numbers of iteration of process − with replacement distribution efficient k of crystallization on separation factor α of distillation.[15]

Other types

- The process of reactive distillation involves using the reaction vessel as the still. In this process, the product is usually significantly lower-boiling than its reactants. As the product is formed from the reactants, it is vaporized and removed from the reaction mixture. This technique is an example of a continuous vs. a batch process; advantages include less downtime to charge the reaction vessel with starting material, and less workup.
- Catalytic distillation is the process by which the reactants are catalyzed while being distilled to continuously separate the products from the reactants. This method is used to assist equilibrium reactions reach completion.
- Pervaporation is a method for the separation of mixtures of liquids by partial vaporization through a non-porous membrane.
- Extractive distillation is defined as distillation in the presence of a miscible, high boiling, relatively non-volatile component, the solvent, that forms no azeotrope with the other components in the mixture.
- Flash evaporation (or partial evaporation) is the partial vaporization that occurs when a saturated liquid stream undergoes a reduction in pressure by passing through a throttling valve or other throttling device. This process is one of the simplest unit operations, being equivalent to a distillation with only one equilibrium stage.
- Codistillation is distillation which is performed on mixtures in which the two compounds are not miscible.

The unit process of evaporation may also be called "distillation":

- In rotary evaporation a vacuum distillation apparatus is used to remove bulk solvents from a sample. Typically the vacuum is generated by a water aspirator or a membrane pump.
- In a kugelrohr a short path distillation apparatus is typically used (generally in combination with a (high) vacuum) to distill high boiling (> 300 °C) compounds. The apparatus consists of an oven in which the compound to be distilled is placed, a receiving portion which is outside of the oven, and a means of rotating the sample. The vacuum is normally generated by using a high vacuum pump.

Other uses:

- Dry distillation or destructive distillation, despite the name, is not truly distillation, but rather a chemical reaction known as pyrolysis in which solid substances are heated in an inert or reducing atmosphere and any volatile fractions, containing high-boiling liquids and products of pyrolysis, are collected. The destructive distillation of wood to give methanol is the root of its common name − *wood alcohol*.
- Freeze distillation is an analogous method of purification using freezing instead of evaporation. It is not truly distillation, but a recrystallization where the product is the mother liquor, and does not produce products equivalent to distillation. This process is used in the production of ice beer and ice wine to increase ethanol and sugar content, respectively. It is also used to produce applejack. Unlike distillation, freeze distillation concentrates poisonous congeners rather than removing them; As a result, many countries prohibit such applejack as a health measure. However, reducing methanol with the absorption of 4A molecular sieve is a practical method for production.[16] Also, distillation by evaporation can separate these since they have different boiling points.

Azeotropic distillation

Interactions between the components of the solution create properties unique to the solution, as most processes entail nonideal mixtures, where Raoult's law does not hold. Such interactions can result in a constant-boiling **azeotrope** which behaves as if it were a pure compound (i.e., boils at a single temperature instead of a range). At an azeotrope, the solution contains the given component in the same proportion as the vapor, so that evaporation does not change the purity, and distillation does not effect separation. For example, ethyl alcohol and water form an azeotrope of 95.6% at 78.1 °C.

If the azeotrope is not considered sufficiently pure for use, there exist some techniques to break the azeotrope to give a pure distillate. This set of techniques are known as **azeotropic distillation**. Some techniques achieve this by "jumping" over the azeotropic composition (by adding an additional component to create a new azeotrope, or by varying the pressure). Others work by chemically or physically removing or sequestering the impurity. For example, to purify ethanol beyond 95%, a drying agent or a (desiccant such as potassium carbonate) can be added to convert the soluble water into insoluble water of crystallization. Molecular sieves are often used for this purpose as well.

Immiscible liquids, such as water and toluene, easily form azeotropes. Commonly, these azeotropes are referred to as a low boiling azeotrope because the boiling point of the azeotrope is lower than the boiling point of either pure component. The temperature and composition of the azeotrope is easily predicted from the vapor pressure of the pure components, without use of Raoult's law. The azeotrope is easily broken in a distillation set-up by using a liquid-liquid separator (a decanter) to separate the two liquid layers that are condensed overhead. Only one of the two liquid layers is refluxed to the distillation set-up.

High boiling azeotropes, such as a 20 weight percent mixture of hydrochloric acid in water, also exist. As implied by the name, the boiling point of the azeotrope is greater than the boiling point of either pure component.

To break azeotropic distillations and cross distillation boundaries, such as in the DeRosier Problem, it is necessary to increase the composition of the light key in the distillate.

Breaking an azeotrope with unidirectional pressure manipulation

The boiling points of components in an azeotrope overlap to form a band. By exposing an azeotrope to a vacuum or positive pressure, it's possible to bias the boiling point of one component away from the other by exploiting the differing vapour pressure curves of each; the curves may overlap at the azeotropic point, but are unlikely to be remain identical further along the pressure axis either side of the azeotropic point. When the bias is great enough, the two boiling points no longer overlap and so the azeotropic band disappears.

This method can remove the need to add other chemicals to a distillation, but it has two potential drawbacks.

Under negative pressure, power for a vacuum source is needed and the reduced boiling points of the distillates requires that the condenser be run cooler to prevent distillate vapours being lost to the vacuum source. Increased cooling demands will often require additional energy and possibly new equipment or a change of coolant.

Alternatively, if positive pressures are required, standard glassware can not be used, energy must be used for pressurization and there is a higher chance of side reactions occurring in the distillation, such as decomposition, due to the higher temperatures required to effect boiling.

A unidirectional distillation will rely on a pressure change in one direction, either positive or negative.

Pressure-swing distillation

Pressure-swing distillation is essentially the same as the unidirectional distillation used to break azeotropic mixtures, but here both positive and negative pressures may be employed. Wikipedia:Please clarify

This has an important impact on the selectivity of the distillation and allows a chemist [*citation needed*] to optimize a process such that fewer extremes of pressure and temperature are required and less energy is consumed. This is particularly important in commercial applications.

Pressure-swing distillation is employed during the industrial purification of ethyl acetate after its catalytic synthesis from ethanol.

Industrial distillation

Large scale **industrial distillation** applications include both batch and continuous fractional, vacuum, azeotropic, extractive, and steam distillation. The most widely used industrial applications of continuous, steady-state fractional distillation are in petroleum refineries, petrochemical and chemical plants and natural gas processing plants.

Industrial distillation[][] is typically performed in large, vertical cylindrical columns known as **distillation towers** or **distillation columns** with diameters ranging from about 65 centimeters to 16 meters and heights ranging from about 6 meters to 90 meters or more. When the process feed has a diverse composition, as in distilling crude oil, liquid outlets at intervals up the column allow for the withdrawal of different *fractions* or products having different boiling points or boiling ranges. The "lightest" products (those with the lowest boiling point) exit from the top of the columns and the "heaviest" products (those with the highest boiling point) exit from the bottom of the column and are often called the **bottoms**.

Typical industrial distillation towers

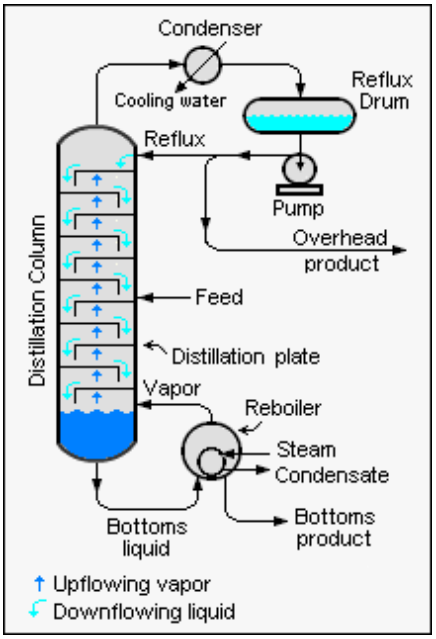
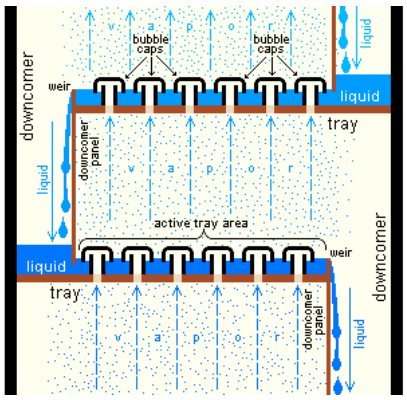


Diagram of a typical industrial distillation tower

Industrial towers use reflux to achieve a more complete separation of products. Reflux refers to the portion of the condensed overhead liquid product from a distillation or fractionation tower that is returned to the upper part of the tower as shown in the schematic diagram of a typical, large-scale industrial distillation tower. Inside the tower, the downflowing reflux liquid provides cooling and condensation of the upflowing vapors thereby increasing the efficiency of the distillation tower. The more reflux that is provided for a given number of theoretical plates, the better the tower's separation of lower boiling materials from higher boiling materials. Alternatively, the more reflux that is provided for a given desired separation, the fewer the number of theoretical plates required.

Such industrial fractionating towers are also used in air separation, producing liquid oxygen, liquid nitrogen, and high purity argon. Distillation of chlorosilanes also enables the production of high-purity silicon for use as a semiconductor.

Design and operation of a distillation tower depends on the feed and desired products. Given a simple, binary component feed, analytical methods such as the McCabe-Thiele method[][] or the Fenske equation[] can be used. For a multi-component feed, simulation models are used both for design and operation. Moreover, the efficiencies of the vapor-liquid contact devices (referred to as "plates" or "trays") used in distillation towers are typically lower than that of a theoretical 100% efficient equilibrium stage. Hence, a distillation tower needs more trays than the number of theoretical vapor-liquid equilibrium stages.



Section of an industrial distillation tower showing detail of trays with bubble caps

In modern industrial uses, a packing material is used in the column instead of trays when low pressure drops across the column are required. Other factors that favor packing are: vacuum systems, smaller diameter columns, corrosive systems, systems prone to foaming, systems requiring low liquid holdup and batch distillation. Conversely, factors that favor plate columns are: presence of solids in feed, high liquid rates, large column diameters, complex columns, columns with wide feed composition variation, columns with a chemical reaction, absorption columns, columns limited by foundation weight tolerance, low liquid rate, large turn-down ratio and those processes subject to process surges.

Large-scale, industrial vacuum distillation column[17]

This packing material can either be random dumped packing (1–3" wide) such as Raschig rings or structured sheet metal. Liquids tend to wet the surface of the packing and the vapors pass across this wetted surface, where mass transfer takes place. Unlike conventional tray distillation in which every tray represents a separate point of vapor-liquid equilibrium, the vapor-liquid equilibrium curve in a packed column is continuous. However, when modeling packed columns, it is useful to compute a number of "theoretical stages" to denote the separation efficiency of the packed column with respect to more traditional trays. Differently shaped packings have different surface areas and void space between packings. Both of these factors affect packing performance.

Another factor in addition to the packing shape and surface area that affects the performance of random or structured packing is the liquid and vapor distribution entering the packed bed. The number of theoretical stages required to make a given separation is calculated using a specific vapor to liquid ratio. If the liquid and vapor are not evenly distributed across the superficial tower area as it enters the packed bed, the liquid to vapor ratio will not be correct in the packed bed and the required separation will not be achieved. The packing will appear to not be working properly. The height equivalent of a theoretical plate (HETP) will be greater than expected. The problem is not the packing itself but the mal-distribution of the fluids entering the packed bed. Liquid mal-distribution is more frequently the problem than vapor. The design of the liquid distributors used to introduce the feed and reflux to a packed bed is critical to making the packing perform to it maximum efficiency. Methods of evaluating the effectiveness of a liquid distributor to evenly distribute the liquid entering a packed bed can be found in references.[18][] Considerable work as been done on this topic by Fractionation Research, Inc. (commonly known as FRI).[]

Multi-effect distillation

The goal of multi-effect distillation is to increase the energy efficiency of the process, for use in desalination, or in some cases one stage in the production of ultrapure water. The number of effects is proportional to the $kW \cdot h/m^3$ of water recovered figure, and refers to the volume of water recovered per unit of energy compared with single-effect distillation. One effect is roughly 636 $kW \cdot h/m^3$.

- Multi-stage flash distillation Can achieve more than 20 effects with thermal energy input, as mentioned in the article.
- Vapor compression evaporation Commercial large-scale units can achieve around 72 effects with electrical energy input, according to manufacturers.

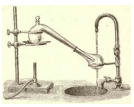
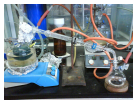
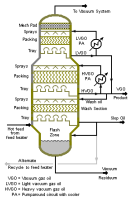
There are many other types of multi-effect distillation processes, including one referred to as simply multi-effect distillation (MED), in which multiple chambers, with intervening heat exchangers, are employed.

Distillation in food processing

Distilled beverages

Carbohydrate-containing plant materials are allowed to ferment, producing a dilute solution of ethanol in the process. Spirits such as whiskey and rum are prepared by distilling these dilute solutions of ethanol. Components other than ethanol, including water, esters, and other alcohols, are collected in the condensate, which account for the flavor of the beverage.

Gallery

	Chemistry in its beginnings used retorts as laboratory equipment exclusively for distillation processes.
	A simple set-up to distill dry and oxygen-free toluene.
	Diagram of an industrial-scale vacuum distillation column as commonly used in oil refineries
	A rotary evaporator is able to distill solvents more quickly at lower temperatures through the use of a vacuum.
	Distillation using semi-microscale apparatus. The jointless design eliminates the need to fit pieces together. The pear-shaped flask allows the last drop of residue to be removed, compared with a similarly-sized round-bottom flask The small holdup volume prevents losses. A pig is used to channel the various distillates into three receiving flasks. If necessary the distillation can be carried out under vacuum using the vacuum adapter at the pig.

Notes

[3] Magnum Opus Hermetic Sourceworks Series (http://www.alchemywebsite.com/bookshop/mohs32.html)

[4] http://www.levity.com/alchemy/jfren_ar.html

[5] *Industrial Engineering Chemistry* (1936) page 677

[6] Sealing Technique (http://www.copper-alembic.com/manufacturing/specs_sealing.php), accessed 16 November 2006.

[7] Traditional Alembic Pot Still (http://www.essentialoil.com/alembic5.html), accessed 16 November 2006.

[8] D. F. Othmer (1982) *Distillation – Some Steps in its Development*, in W. F. Furter (ed) *A Century of Chemical Engineering* ISBN 0-306-40895-3

[9] A. Coffey British Patent 5974, 5 August 1830

[10] Improvement in the Ammonia-Soda Manufacture

[11] ST07 Separation of liquid–liquid mixtures (solutions) (http://www.iupac.org/didac/Didac Eng/Didac05/Content/ST07.htm), DIDAC by IUPAC

[12] Fractional Distillation (http://wulfenite.fandm.edu/labtech/fractdistill.htm)

[13] Spinning Band Distillation (http://www.brinstrument.com/fractional-distillation/spinning_band_distillation.html) at B/R Instrument Corporation (accessed 8 September 2006)

[14] Vogel's 5th ed.

[16] http://124.205.222.100/Jwk_spkx/EN/abstract/abstract15544.shtml

[17] Energy Institute website page (http://resources.schoolscience.co.uk/SPE/knowl/4/2index.htm?vacuum.html)

[18] *Random Packing, Vapor and Liquid Distribution: Liquid and gas distribution in commercial packed towers*, Moore, F., Rukovena, F., Chemical Plants & Processing, Edition Europe, August 1987, p. 11-15

Further reading

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- Geankoplis, Christie John (2003). *Transport Processes and Separation Process Principles* (4th ed.). Prentice Hall. ISBN 0-13-101367-X.

External links

- Alcohol distillation (http://www.agcom.purdue.edu/AgCom/Pubs/AE/AE-117.html)
- Case Study: Petroleum Distillation (http://www.members.tripod.com/historycheme/h_distill.html)
- "Binary Vapor-Liquid Equilibrium Data" (http://www.cheric.org/research/kdb/hcvle/hcvle.php) (searchable database). Chemical Engineering Research Information Center. Retrieved 5 May 2007.

Essential oil

An **essential oil** is a concentrated hydrophobic liquid containing volatile aroma compounds from plants. Essential oils are also known as **volatile oils**, **ethereal oils** or **aetherolea**, or simply as the "oil of" the plant from which they were extracted, such as oil of clove. An oil is "essential" in the sense that it carries a distinctive scent, or essence, of the plant. Essential oils do not form a distinctive category for any medical, pharmacological, or culinary purpose.

A glass vial containing sandalwood oil

Essential oils are generally extracted by distillation. Steam distillation is often used. Other processes include expression or solvent extraction. They are used in perfumes, cosmetics, soaps and other products, for flavoring food and drink, and for adding scents to incense and household cleaning products.

Essential oils have been used medicinally in history. Medical applications proposed by those who sell medicinal oils range from skin treatments to remedies for cancer and often are based solely on historical accounts of use of essential oils for these purposes. Claims for the efficacy of medical treatments, and treatment of cancers in particular, are now subject to regulation in most countries.

As the use of essential oils has declined in evidence-based medicine, one must consult older textbooks for much information on their use.[1][2] Modern works are less inclined to generalize; rather than refer to "essential oils" as a class at all, they prefer to discuss specific compounds, such as methyl salicylate, rather than "oil of wintergreen".[][]

Interest in essential oils has revived in recent decades with the popularity of aromatherapy, a branch of alternative medicine that claims that essential oils and other aromatic compounds have curative effects. Oils are volatilized or diluted in a carrier oil and used in massage, diffused in the air by a nebulizer, heated over a candle flame, or burned as incense.

The earliest recorded mention of the techniques and methods used to produce essential oils is believed to be that of Ibn al-Baitar (1188–1248), an Andalusian physician, pharmacist and chemist.[3]

Production

Distillation

Today, most common essential oils — such as lavender, peppermint, and eucalyptus — are distilled. Raw plant material, consisting of the flowers, leaves, wood, bark, roots, seeds, or peel, is put into an alembic (distillation apparatus) over water. As the water is heated, the steam passes through the plant material, vaporizing the volatile compounds. The vapors flow through a coil, where they condense back to liquid, which is then collected in the receiving vessel.

Most oils are distilled in a single process. One exception is *ylang-ylang* (*Cananga odorata*), which takes 22 hours to complete through a fractional distillation.

The recondensed water is referred to as a hydrosol, hydrolat, herbal distillate or plant water essence, which may be sold as another fragrant product. Popular hydrosols include rose water, lavender water, lemon balm, clary sage and orange blossom water. The use of herbal distillates in cosmetics is increasing. Some plant hydrosols have unpleasant smells and are therefore not sold.

Expression

Most citrus peel oils are expressed mechanically or cold-pressed (similar to olive oil extraction). Due to the relatively large quantities of oil in citrus peel and low cost to grow and harvest the raw materials, citrus-fruit oils are cheaper than most other essential oils. Lemon or sweet orange oils that are obtained as byproducts of the citrus industry are even cheaper.

Before the discovery of distillation, all essential oils were extracted by pressing.

Solvent extraction

Most flowers contain too little volatile oil to undergo expression; their chemical components are too delicate and easily denatured by the high heat used in steam distillation. Instead, a solvent such as hexane or supercritical carbon dioxide is used to extract the oils. Extracts from hexane and other hydrophobic solvent are called *concretes*, which are a mixture of essential oil, waxes, resins, and other lipophilic (oil soluble) plant material.

Although highly fragrant, concretes contain large quantities of nonfragrant waxes and resins. Often, another solvent, such as ethyl alcohol, which is more polar in nature, is used to extract the fragrant oil from the concrete. The alcohol is removed by evaporation, leaving behind the *absolute*.

Supercritical carbon dioxide is used as a solvent in supercritical fluid extraction. This method has many benefits including avoiding petrochemical residues in the product and the loss of some "top notes" when steam distillation is used. It does not yield an absolute directly. The supercritical carbon dioxide will extract both the waxes and the essential oils that make up the concrete. Subsequent processing with liquid carbon dioxide, achieved in the same extractor by merely lowering the extraction temperature, will separate the waxes from the essential oils. This lower temperature process prevents the decomposition and denaturing of compounds. When the extraction is complete, the pressure is reduced to ambient and the carbon dioxide reverts to a gas, leaving no residue. An animated presentation [4] describing the process is available for viewing.

Supercritical carbon dioxide is also used for making decaffeinated coffee. Although it uses the same basic principles, it is a different process because of the difference in scale.

Florasols extraction

Florasol (R134a), a refrigerant, was developed to replace Freon. Florasol is an ozone friendly product and it poses little danger to the environment. One advantage is that the extraction of essential oils occurs at or below room temperature so degradation through high temperature extremes does not occur. The essential oils are mostly pure and contain little to no foreign substances. [*citation needed*]

Production quantities

Estimates of total production of essential oils are difficult to obtain. One estimate, compiled from data in 1989, 1990 and 1994 from various sources, gives the following total production, in tonnes, of essential oils for which more than 1,000 tonnes were produced.[5]

Oil	Tonnes
Sweet orange	12,000
Mentha arvensis	4,800
Peppermint	3,200
Cedarwood	2,600
Lemon	2,300
Eucalyptus globulus	2,070
Litsea cubeba	2,000
Clove (leaf)	2,000
Spearmint	1,300

Pharmacology

Although some are suspicious or dismissive towards the use of essential oils in healthcare or pharmacology,[6] essential oils retain considerable popular use, partly in fringe medicine and partly in popular remedies. Therefore it is difficult to obtain reliable references concerning their pharmacological merits.

Studies have shown that certain essential oils may have the ability to prevent the transmission of some drug-resistant strains of pathogen, specifically Staphylococcus, Streptococcus and Candida.[]

Taken by mouth, many essential oils can be dangerous in high concentrations. Typical effects begin with a burning feeling, followed by salivation. In the stomach, the effect is carminative, relaxing the gastric sphincter and encouraging eructation (belching). Further down the gut, the effect typically is antispasmodic.[1]

Typical ingredients for such applications include eucalyptus oils, menthol, capsaicin, anise and camphor. Other essential oils work well in these applications, but it is notable that others offer no significant benefit. This illustrates the fact that different essential oils may have drastically different pharmacology. Those that do work well for upper respiratory tract and bronchial problems act variously as mild expectorants and decongestants. Some act as locally anaesthetic counterirritants and, thereby, exert an antitussive effect.[1][7]

Some essential oils, such as those of juniper and agathosma, are valued for their diuretic effects.[8] With relatively recent concerns about the overuse of antibacterial agents,[9] many essential oils[10] have seen a resurgence in off-label use[10] for such properties and are being examined for this use clinically.[11]

Many essential oils affect the skin and mucous membranes in ways that are valuable or harmful. They are used in antiseptics and liniments in particular. Typically, they produce rubefacient irritation at first and then counterirritant numbness. Turpentine oil and camphor are two typical examples of oils that cause such effects. Menthol and some others produce a feeling of cold followed by a sense of burning. This is caused by its effect on heat-sensing nerve endings. Some essential oils, such as clove oil or eugenol, were popular for many years in dentistry as antiseptics and local anaesthetics. Thymol is well known for its antiseptic effects.

Use in aromatherapy

Aromatherapy is a form of alternative medicine in which healing effects are ascribed to the aromatic compounds in essential oils and other plant extracts. Many common essential oils have medicinal properties that have been applied in folk medicine since ancient times and are still widely used today. For example, many essential oils have antiseptic properties.[12] Many are also claimed to have an uplifting effect on the mind. Such claims, if meaningful, are not necessarily false but are difficult to quantify in the light of the sheer variability of materials used in the practice.

Dilution

Essential oils are usually lipophilic (literally: *"oil-loving"*) compounds that usually are not miscible with water. Also, they can be diluted in solvents like pure ethanol, and polyethylene glycol.

Raw materials

Essential oils are derived from sections of plants. Some plants, like the bitter orange, are sources of several types of essential oil.

Berries
- Allspice
- Juniper

Seeds
- Almond
- Anise
- Buchu
- Celery
- Cumin
- Nutmeg oil

Bark
- Cassia
- Cinnamon
- Sassafras

Wood
- Camphor
- Cedar
- Rosewood
- Sandalwood
- Agarwood

Rhizome
- Galangal
- Ginger

Leaves
- Basil
- Bay leaf
- Buchu
- Cinnamon
- Common sage
- Eucalyptus
- Guava
- Lemon grass
- Melaleuca
- Oregano
- Patchouli
- Peppermint
- Pine
- Rosemary
- Spearmint
- Tea tree
- Thyme
- Tsuga
- Wintergreen

Resin
- Benzoin
- Copaiba
- Frankincense
- Myrrh

Flowers
- Cannabis
- Chamomile
- Clary sage
- Clove
- Scented geranium
- Hops
- Hyssop
- Jasmine
- Lavender
- Manuka
- Marjoram
- Orange
- Rose
- Ylang-ylang

Peel
- Bergamot
- Grapefruit
- Lemon
- Lime
- Orange
- Tangerine

Root
- Valerian

Eucalyptus oil

Apart from essential oils used mainly in foods, the best-known essential oil worldwide might be eucalyptus oil, produced from the leaves of *Eucalyptus globulus*. Steam-distilled eucalyptus oil is used throughout Asia, Africa, Latin America and South America as a primary cleaning/disinfecting agent added to soaped mop and countertop cleaning solutions; it also possesses insect and limited vermin control properties. Note, however, there are hundreds of species of eucalyptus, and perhaps some dozens are used to various extents as sources of essential oils. Not only do the products of different species differ greatly in characteristics and effects, but also the products of the very same tree can vary grossly.[2]

Rose oil

The second most well-known essential oil is probably rose oil, produced from the petals of *Rosa damascena* and *Rosa centifolia*. Steam-distilled rose oil is known as "rose otto", while the solvent extracted product is known as "rose absolute".

Lavender essential oil

One of the most popular essential oils in the world, lavender essential oil has a reputation of being mild, relaxing and appropriate for all ages and genders. Lavender essential oil is also an insect repellant.[*citation needed*]

Dangers

The potential danger of an essential oil is generally relative to its level or grade of purity. Many essential oils are designed exclusively for their aroma-therapeutic quality; these essential oils generally should not be applied directly to the skin in their undiluted or "neat" form. Some can cause severe irritation, provoke an allergic reaction and, over time, prove hepatotoxic. Non-therapeutic grade essential oils are never recommended for topical or internal use.

Essential oils should not be used with animals, as they possess extreme hepatotoxicity and dermal toxicity for animals, especially for cats. Instead, essential oils should be blended with a vegetable-based carrier oil (as a base, or "fixed" oil) before being applied. Common carrier oils include olive, almond, hazelnut and grapeseed. Only neutral oils should be used. A common ratio of essential oil disbursed in a carrier oil is 0.5%–3% (most under 10%), depending on its purpose. Some essential oils, including many of the citrus peel oils, are photosensitizers, increasing the skin's vulnerability to sunlight.

Industrial users of essential oils should consult the material safety data sheets (MSDS) to determine the hazards and handling requirements of particular oils. Even certain therapeutic grade oils can pose potential threats to individuals with epilepsy or pregnant women.

Handling

Essential oils can be aggressive toward rubbers and plastics, so care must be taken in choosing the correct handling equipment. Glass syringes are often used, but have coarse volumetric graduations. Chemistry syringes are ideal, as they resist essential oils, are long enough to enter deep vessels, and have fine graduations, facilitating quality control. Unlike traditional pipettes, which have difficulty handling viscous fluids, the chemistry syringe has a seal and piston arrangement which slides inside the pipette, wiping the essential oil off the pipette wall. This improves accuracy, and the inside of the pipette is easy to clean and reuse immediately. Chemistry pipetting syringes are equal in accuracy to the best laboratory equipment and are available in sizes from 1 mL through 25 mL.

Pregnancy

The use of essential oils in pregnancy is not recommended due to inadequate published evidence to demonstrate evidence of safety.[*citation needed*] Pregnant women often report an abnormal sensitivity to smells and taste,[13] essential oils can cause irritation and nausea.

Gynecomastia

Estrogenic and antiandrogenic activity have been reported by *in vitro* study of tea tree oil and lavender essential oils. Case reports suggest the oils may be implicated in some cases of gynecomastia, an abnormal breast tissue growth, in prepubescent boys.[14][15]

Pesticide residues

There is some concern about pesticide residues in essential oils, particularly those used therapeutically. For this reason, many practitioners of aromatherapy buy organically produced oils.[*citation needed*] Not only are pesticides present in trace quantities, but also the oils themselves are used in tiny quantities and usually in high dilutions. Where there is a concern about pesticide residues in food essential oils, such as mint or orange oils, the proper criterion is not whether the material is alleged to be organically produced, but whether it meets the government standards based on actual analysis of its pesticide content.[16]

Ingestion

Essential oils are used extensively as GRAS flavoring agents in foods, beverages and confectioneries according to strict Good Manufacturing Practice (GMP) and flavorist standards. Therapeutic grade essential oils are generally safe for human consumption in small amounts. Pharmacopoeia standards for medicinal oils should be heeded. Some oils can be toxic to some domestic animals, cats in particular.[17] The internal use of essential oils can pose hazards to pregnant women, as some can be abortifacients in dose 0.5–10 ml, and thus should not be used during pregnancy.

Flammability

The flash point of each essential oil is different. Many of the common essential oils, such as tea tree, lavender, and citrus oils, are classed as a Class 3 Flammable Liquid, as they have a flash point of 50–60 °C.

Toxicology

The following table lists the LD_{50} or median lethal dose for common oils; this is the dose required to kill half the members of a tested population.LD_{50} is intended as a guideline only, and reported values can vary widely due to differences in tested species and testing conditions.[18]

Common Name	Oral LD_{50}	Dermal LD_{50}	Notes
Neem	14 g/kg	>2 g/kg	
Lemon myrtle	2.43 g/kg	2.25 g/kg	
Frankincense	>5 g/kg	>5 g/kg	*Boswellia carterii*
Frankincense	>2 g/kg	>2 g/kg	*Boswellia sacra*
Indian frankincense	>2 g/kg	>2 g/kg	*Boswellia serrata*
Ylang-ylang	>5 g/kg	>5 g/kg	
Cedarwood	>5 g/kg	>5 g/kg	
Roman chamomile	>5 g/kg	>5 g/kg	
White camphor	>5 g/kg	>5 g/kg	*Cinnamomum camphora*, extracted from leaves

Yellow camphor	3.73 g/kg	>5 g/kg	*Cinnamomum camphora*, extracted from bark
Hot oil	3.80 g/kg	>5 g/kg	*Cinnamomum camphora*, oil extracted from leaves
Cassia	2.80 g/kg	0.32 g/kg	

It is important to understand that the foregoing figures are far less relevant in everyday life than far smaller, often localized levels of exposure. For example, a dose of many an essential oil that would do no harm if swallowed in diluted solution or emulsion, could do serious damage to eyes or lungs in a higher concentration.[1]

Standardization of its derived products

In 2002, ISO published ISO 4720 in which the botanical names of the relevant plants are standardized.[] The rest of the standards with regards to this topic can be found in the section of ICS 71.100.60 []

Notes

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External links

Media related to Essential oils at Wikimedia Commons

Hash oil

Hash oil (also known as **honey oil**, **dabs**, **shatter**, or **earwax**) is a resinous matrix of cannabinoids obtained from the cannabis plant by solvent extraction.[1]

Hash oil is the most potent of three main cannabis products, which are herb (marijuana), resin (hashish), and oil (hash oil).[]

Closeup image of a drop of **hash oil** on the end of a needle.

THC contents

Reported THC contents vary between sources. The 2009 World Drug Reports reports THC content as "may exceed 60%". A 2013 American forensic science book gave a range of 10-30% delta-9 THC by weight.[2] and a 1972 American forensic journal reported a range of 20-65%.[3]

Usage

Hash oil can be consumed in various ways, including smoking, vaporization, or orally.[4]

Manufacturing

Hash oil is a cannabis product obtained from separating resins from leaves by solvent extraction.[5]

Cannabis is boiled in a solvent to form a viscous liquid which is then strained and the solvent is evaporated to yield hash oil. Flammable solvents used in extraction makes the process dangerous.[6]

Newer methods like CO2 extraction provide a safer way to extract the resin. CO2 extraction is a method of using high pressure to force a solvent through plant matter. The solvent used for extraction is carbon dioxide. The solvent is pushed through the plant matter at a high pressure and separates the cannabinoid resins and terpenes from the plant matter. The result is pure, transparent, amber oil. Carbon Dioxide is a natural product which leaves behind no residues. CO2's purity is its biggest advantage over all other solvents used for plant extraction. Currently, a popular extraction solvent is butane which can potentially leave heavy metals behind in the extracted product.

Social concerns

Explosion and fire incidents related to manufacturing attempts in homes have been reported. Associated Press reports that such incidents in United States have primarily been in west coast states that permit medical marijuana.[]

Legality

Cannabis extracts (including hash oil) are classified as narcotic drugs under Schedule I and IV of the 1961 United Nations Single Convention on Narcotic Drugs.[]

Statistics

The 2006 *World Drug Report* reports that cannabis oil seizures doubled in 2004, and that it represented 0.01% of global cannabis seized.[7] In 2007, 418 kg equivalent of hash oil was seized globally.[8]

Australia

In the Northern Territory, adults found in possession of up to one gram of hash oil can face a fine of up to $200, which if paid within 28 days, negates a criminal charge.[9]

Under New Zealand law hashish, hash oil, THC, and any other preparations containing THC made by processing the plant are scheduled as Class B substances.[]

Italy

issues a warning to those in possession of a substance for personal use which contains up to one gram of THC, with further sanctions following if the subject re-offends.[]

Portugal

Although provision of tools utilized in production and consumption of cannabis is illegal in Portugal; Portuguese law allows for the possession of up to 2.5 grams of hash oil for personal use.

United States

The production or possession of hash is illegal in many US states without medical marijuana. States such as Texas as well as others consider hash as a controlled substance and is a felony offense. Until guidelines were amended in November 1995, Federal law did not explicitly define the difference between marijuana, hash, and hash oil, which led to cannabis preparations being assessed case-by-case.[10] Under the new federal guidelines, *hashish oil* is characterized as:

> A preperation of the soluble cannabinioids derived from *Cannabis* that includes (i) one or more of the tetrahydrocannibinols.. ..and (ii) at least two of the following: cannabinol, cannabidiol, or cannibichromene, and (iii) is essentially free of plant material.[11]

United Kingdom

Hashish is classified as a Class B controlled substance under the Misuse of Drugs Act 1971. The status of "liquid cannabis" is "currently the subject of legal argument"[12] *The Misuse of Drugs Act: A Guide For Forensic Scientists* published by the Royal Society of Chemistry suggests that the term "liquid cannabis" is preferable to "hash oil", as it does not involve definition of what exactly constitutes an "oil". The authors also recommend adoption of "purified form" instead of "solvent extract" when describing hash oil, as the former would not require proof of solvent usage by forensic scientists.[13]

Images

Hash oil

Hash oil

Golden cannabis oil

Full extract oil in oral syringe

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Further reading

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Liquid–liquid extraction

Liquid–liquid extraction, also known as **solvent extraction** and **partitioning**, is a method to separate compounds based on their relative solubilities in two different immiscible liquids, usually water and an organic solvent. It is an extraction of a substance from one liquid into another liquid phase. Liquid–liquid extraction is a basic technique in chemical laboratories, where it is performed using a separatory funnel. This type of process is commonly performed after a chemical reaction as part of the work-up.

The term *partitioning* is commonly used to refer to the underlying chemical and physical processes involved in *liquid–liquid extraction* but may be fully synonymous. The term *solvent extraction* can also refer to the separation of a substance from a mixture by preferentially dissolving that substance in a suitable solvent. In that case, a soluble compound is separated from an insoluble compound or a complex matrix.

Solvent extraction is used in nuclear reprocessing, ore processing, the production of fine organic compounds, the processing of perfumes, the production of vegetable oils and biodiesel, and other industries.

Liquid–liquid extraction is possible in non-aqueous systems: In a system consisting of a molten metal in contact with molten salts, metals can be extracted from one phase to the other. This is related to a mercury electrode where a metal can be reduced, the metal will often then dissolve in the mercury to form an amalgam that modifies its electrochemistry greatly. For example, it is possible for sodium cations to be reduced at a mercury cathode to form sodium amalgam, while at an inert electrode (such as platinum) the sodium cations are not reduced. Instead, water is reduced to hydrogen. A detergent or fine solid can be used to stabilize an emulsion, or third phase.

Measures of effectiveness

Distribution ratio

In solvent extraction, a distribution ratio is often quoted as a measure of how well-extracted a species is. The distribution ratio (D) is equal to the concentration of a solute in the organic phase divided by its concentration in the aqueous phase. Depending on the system, the distribution ratio can be a function of temperature, the concentration of chemical species in the system, and a large number of other parameters.

Note that D is related to the ΔG of the extraction process.

Sometimes, the distribution ratio is referred to as the partition coefficient, which is often expressed as the logarithm. Note that a distribution ratio for uranium and neptunium between two inorganic solids (zirconolite and perovskite) has been reported.[1] In solvent extraction, two immiscible liquids are shaken together. The more polar solutes dissolve preferentially in the more polar solvent, and the less polar solutes in the less polar solvent. In this experiment, the nonpolar halogens preferentially dissolve in the nonpolar mineral oil.

Separation factors

The separation factor is one distribution ratio divided by another; it is a measure of the ability of the system to separate two solutes. For instance, if the distribution ratio for nickel (D_{Ni}) is 10 and the distribution ratio for silver (D_{Ag}) is 100, then the silver/nickel separation factor ($SF_{Ag/Ni}$) is equal to $D_{Ag}/D_{Ni} = SF_{Ag/Ni} = 10$.

Decontamination factor

This is used to express the ability of a process to remove a contaminant from a product. For instance, if a process is fed with a mixture of 1:9 cadmium to indium, and the product is a 1:99 mixture of cadmium and indium, then the decontamination factor (for the removal of cadmium) of the process is 0.1 / 0.01 = 10.

Slopes of graphs

The easy way to work out the extraction mechanism is to draw graphs and measure the slopes. If for an extraction system the *D* value is proportional to the square of the concentration of a reagent (*Z*) then the slope of the graph of $\log_{10}(D)$ against $\log_{10}([[Z]])$ will be two.

Techniques

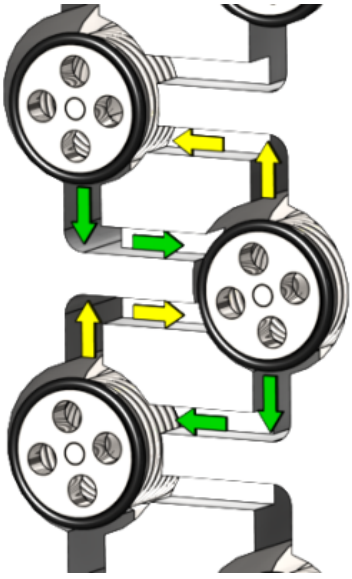
Batchwise single stage extractions

This is commonly used on the small scale in chemical labs. It is normal to use a separating funnel. For instance, if a chemist were to extract anisole from a mixture of water and 5% acetic acid using ether, then the anisole will enter the organic phase. The two phases would then be separated.

The acetic acid can then be scrubbed (removed) from the organic phase by shaking the organic extract with sodium bicarbonate. The acetic acid reacts with the sodium bicarbonate to form sodium acetate, carbon dioxide, and water.

Multistage countercurrent continuous processes

These are commonly used in industry for the processing of metals such as the lanthanides; because the separation factors between the lanthanides are so small many extraction stages are needed. In the multistage processes, the aqueous raffinate from one extraction unit is fed to the next unit as the aqueous feed, while the organic phase is moved in the opposite direction. Hence, in this way, even if the separation between two metals in each stage is small, the overall system can have a higher decontamination factor.



Coflore continuous countercurrent extractor

Multistage countercurrent arrays have been used for the separation of lanthanides. For the design of a good process, the distribution ratio should be not too high (>100) or too low (<0.1) in the extraction portion of the process. It is often the case that the process will have a section for scrubbing unwanted metals from the organic phase, and finally a stripping section to obtain the metal back from the organic phase.

Multistage Podbielniak contactor centrifuges produce three to five stages of theoretical extraction in a single countercurrent pass, and are used in fermentation-based pharmaceutical and food additive production facilities.

Centrifugal extractors mix and separate in one unit. Two liquids will be intensively mixed between the spinning rotor and the stationary housing at speeds up to 6000 RPM. This develops great surfaces for an ideal mass transfer from the aqueous phase into the organic phase. At 200 − 2000 g both phases will be separated again. Centrifugal extractors minimize the solvent in the process, optimize the product load in the solvent and extract the aqueous phase completely. Counter current and cross current extractions are easily established.

Extraction without chemical change

Some solutes such as noble gases can be extracted from one phase to another without the need for a chemical reaction (see absorption). This is the simplest type of solvent extraction. When a solvent is extracted, two immiscible liquids are shaken together. The more polar solutes dissolve preferentially in the more polar solvent, and the less polar solutes in the less polar solvent. Some solutes that do not at first sight appear to undergo a reaction during the extraction process do not have distribution ratio that is independent of concentration. A classic example is the extraction of carboxylic acids (**HA**) into nonpolar media such as benzene. Here, it is often the case that the carboxylic acid will form a dimer in the organic layer so the distribution ratio will change as a function of the acid concentration (measured in either phase).

For this case, the extraction constant k is described by k = '"HA"'_{organic}^{2}/'"HA"'_{aqueous}

Solvation mechanism

Using solvent extraction it is possible to extract uranium, plutonium, or thorium from acid solutions. One solvent used for this purpose is the organophosphate tri-n-butyl phosphate. The PUREX process that is commonly used in nuclear reprocessing uses a mixture of tri-n-butyl phosphate and an inert hydrocarbon (kerosene), the uranium(VI) are extracted from strong nitric acid and are back-extracted (stripped) using weak nitric acid. An organic soluble uranium complex $[UO_2(TBP)_2(NO_3)_2]$ is formed, then the organic layer bearing the uranium is brought into contact with a dilute nitric acid solution; the equilibrium is shifted away from the organic soluble uranium complex and towards the free TBP and uranyl nitrate in dilute nitric acid. The plutonium(IV) forms a similar complex to the uranium(VI), but it is possible to strip the plutonium in more than one way; a reducing agent that converts the plutonium to the trivalent oxidation state can be added. This oxidation state does not form a stable complex with TBP and nitrate unless the nitrate concentration is very high (circa 10 mol/L nitrate is required in the aqueous phase). Another method is to simply use dilute nitric acid as a stripping agent for the plutonium. This PUREX chemistry is a classic example of a solvation extraction.

Here in this case D_U = k TBP^{2}NO₃^{2}

Ion exchange mechanism

Another extraction mechanism is known as the ion exchange mechanism. Here, when an ion is transferred from the aqueous phase to the organic phase, another ion is transferred in the other direction to maintain the charge balance. This additional ion is often a hydrogen ion; for ion exchange mechanisms, the distribution ratio is often a function of pH. An example of an ion exchange extraction would be the extraction of americium by a combination of terpyridine and a carboxylic acid in *tert*-butyl benzene. In this case

$D_{Am} = k$ terpyridine^{1}carboxylic acid^{3}H+$^{-3}$

Another example is the extraction of zinc, cadmium, or lead by a dialkyl phosphinic acid (R_2PO_2H) into a nonpolar diluent such as an alkane. A non-polar diluent favours the formation of uncharged non-polar metal complexes.

Some extraction systems are able to extract metals by both the solvation and ion exchange mechanisms; an example of such a system is the americium (and lanthanide) extraction from nitric acid by a combination of 6,6'-*bis*-(5,6-dipentyl-1,2,4-triazin-3-yl)-2,2'-bipyridine and 2-bromohexanoic acid in *tert*-butyl benzene. At both high- and low-nitric acid concentrations, the metal distribution ratio is higher than it is for an intermediate nitric acid

concentration.

Ion pair extraction

It is possible by careful choice of counterion to extract a metal. For instance, if the nitrate concentration is high, it is possible to extract americium as an anionic nitrate complex if the mixture contains a lipophilic quaternary ammonium salt.

An example that is more likely to be encountered by the *'average'* chemist is the use of a phase transfer catalyst. This is a charged species that transfers another ion to the organic phase. The ion reacts and then forms another ion, which is then transferred back to the aqueous phase.

For instance, the 31.1 kJ mol^{-1} is required to transfer an acetate anion into nitrobenzene,[2] while the energy required to transfer a chloride anion from an aqueous phase to nitrobenzene is 43.8 kJ mol^{-1}.[3] Hence, if the aqueous phase in a reaction is a solution of sodium acetate while the organic phase is a nitrobenzene solution of benzyl chloride, then, when a phase transfer catalyst, the acetate anions can be transferred from the aqueous layer where they react with the benzyl chloride to form benzyl acetate and a chloride anion. The chloride anion is then transferred to the aqueous phase. The transfer energies of the anions contribute to that given out by the reaction.

A 43.8 to 31.1 kJ mol^{-1} = 12.7 kJ mol^{-1} of additional energy is given out by the reaction when compared with energy if the reaction had been done in nitrobenzene using one equivalent weight of a tetraalkylammonium acetate.

Aqueous two-phase extraction

Aqueous two-phase extraction, also known as *two-phase liquid extraction*, is a unique form of solvent extraction. In an aqueous two-phase extraction, compounds are still separated based on their solubility, but the two immiscible phases are both water-based, an aqueous two phase system.

Aqueous two-phase extractions can have a number of advantages over traditional solvent extraction. Solvents are often destructive to proteins, making the traditional extraction impossible for purifying proteins. In addition, organic solvents can be flammable, and their use can cause both environmental and health concerns. Aqueous-two phase extractions do not require solvents, and so avoid these concerns.

Types of aqueous two-phase extractions

Polymer–polymer systems

In a Polymer–polymer system, both phases are generated by a dissolved polymer. The heavy phase will generally be Polyethylene glycol (PEG), and the light phase is generally a polysaccharide. Traditionally, the polymer used is dextran. However, dextran is relatively expensive, and research has been exploring using less expensive polysaccharides to generate the light phase.

If the target compound being separated is a protein or enzyme, it is possible to incorporate a ligand to the target into one of the polymer phases. This improves the target's affinity to that phase, and improves its ability to partition from one phase into the other. This, as well as the absence of solvents or other denaturing agents, makes polymer–polymer extractions an attractive option for purifying proteins.

The two phases of a polymer–polymer system often have very similar densities, and very low surface tension between them. Because of this, demixing a polymer–polymer system is often much more difficult than demixing a solvent extraction. Methods to improve the demixing include centrifugation, and application of an electric field.

Polymer–salt systems

Aqueous two-phase systems can also be generated by introducing a high concentration of salt to a polymer solution. The polymer phase used is generally still PEG. Generally, a kosmotropic salt, such as Na_3PO_4 is used, however PEG–NaCl systems have been documented when the salt concentration is high enough.

Since polymer–salt systems demix readily they are easier to use. However, at high salt concentrations, proteins generally either denature, or precipitate from solution. Thus, polymer–salt systems are not as useful for purifying proteins.

Ionic liquids

Ionic liquids are ionic compounds with low melting points. While they are not technically aqueous, recent research has experimented with using them in an extraction that does not use organic solvents.

Applications

- DNA purification: The ability to purify DNA from a sample is important for many modern biotechnology processes. However, samples often contain nucleases that degrade the target DNA before it can be purified. It has been shown that DNA fragments will partition into the light phase of a polymer–salt separation system. If ligands known to bind and deactivate nucleases are incorporated into the polymer phase, the nucleases will then partition into the heavy phase and be deactivated. Thus, this polymer–salt system is a useful tool for purifying DNA from a sample while simultaneously protecting it from nucleases.
- Food Industry: The PEG–NaCl system has been shown to be effective at partitioning small molecules, such as peptides and nucleic acids. These compounds are often flavorants or odorants. The system could then be used by the food industry to isolate or eliminate particular flavors.

Kinetics of extraction

It is important to investigate the rate at which the solute is transferred between the two phases, in some cases by an alteration of the contact time it is possible to alter the selectivity of the extraction. For instance, the extraction of palladium or nickel can be very slow because the rate of ligand exchange at these metal centers is much lower than the rates for iron or silver complexes.

Aqueous complexing agents

If a complexing agent is present in the aqueous phase then it can lower the distribution ratio. For instance, in the case of iodine being distributed between water and an inert organic solvent such as carbon tetrachloride then the presence of iodide in the aqueous phase can alter the extraction chemistry.

Instead of D_{I+2} being a constant it becomes $D_{I+2} =$ *k*I₂._{Organic}/[$I_{2\cdot Aqueous}$] I⁻._{Aqueous}

This is because the iodine reacts with the iodide to form I_3^-. The I_3^- anion is an example of a polyhalide anion that is quite common.

Industrial process design

In a typical scenario, an industrial process will use an extraction step in which solutes are transferred from the aqueous phase to the organic phase; this is often followed by a scrubbing stage in which unwanted solutes are removed from the organic phase, then a stripping stage in which the wanted solutes are removed from the organic phase. The organic phase may then be treated to make it ready for use again.

After use, the organic phase may be subjected to a cleaning step to remove any degradation products; for instance, in PUREX plants, the used organic phase is washed with sodium carbonate solution to remove any dibutyl hydrogen phosphate or butyl dihydrogen phosphate that might be present.

Equipment

Two layers separating during a liquid–liquid extraction.

While solvent extraction is often done on a small scale by synthetic lab chemists using a separatory funnel or Craig apparatus, it is normally done on the industrial scale using machines that bring the two liquid phases into contact with each other. Such machines include centrifugal contactors, Thin Layer Extraction, spray columns, pulsed columns, and mixer-settlers.

Extraction of metals

The extraction methods for a range of metals include:[4]

- Cobalt – The extraction of cobalt from hydrochloric acid using alamine 336 in *meta*-xylene.[5] Cobalt can be extracted also using Cyanex 272 {*bis*-(2,4,4-trimethylpentyl) phosphinic acid}.
- Copper – Copper can be extracted using hydroxyoximes as extractants, a recent paper describes an extractant that has a good selectivity for copper over cobalt and nickel.[6]
- Neodymium – This rare earth is extracted by di(2-ethyl-hexyl)phosphoric acid into hexane by an ion exchange mechanism.[7]
- Nickel – Nickel can be extracted using di(2-ethyl-hexyl)phosphoric acid and tributyl phosphate in a hydrocarbon diluent (Shellsol).[8]
- Palladium and platinum – Dialkyl sulfides, tributyl phosphate and alkyl amines have been used for extracting these metals.[9][10]
- Zinc and cadmium – The zinc and cadmium are both extracted by an ion exchange process, the *N,N,N′,N′*-tetrakis(2-pyridylmethyl)ethylenediamine (TPEN) acts as a masking agent for the zinc and an extractant for the cadmium.[11] In the modified Zincex process, zinc is separated from most divalent ions by solvent extraction. D2EHPA (Di (2) ethyl hexyl phosphoric acid) is used for this. A zinc ion replaces the proton from two D2EHPA molecules. To strip the zinc from the D2EHPA, sulfuric acid is used, at a concentration of above 170g/l (typically 240-265g/l).

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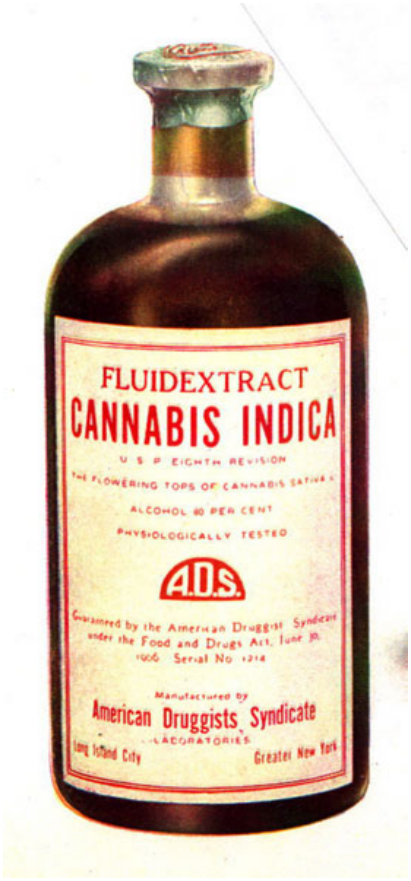
Medical cannabis

Medical cannabis refers to the parts of the herb cannabis used as a physician-recommended form of medicine or herbal therapy, or to synthetic forms of specific cannabinoids such as THC (delta-9-tetrahydrocannabinol) as a physician-recommended form of medicine. The *Cannabis* plant has a long history of use as medicine, with legendary evidence dating back to the Emperor Shen Nung in 2737 BCE.[] Cannabis is one of the 50 "fundamental" herbs of traditional Chinese medicine,[] and is prescribed for a broad range of indications.

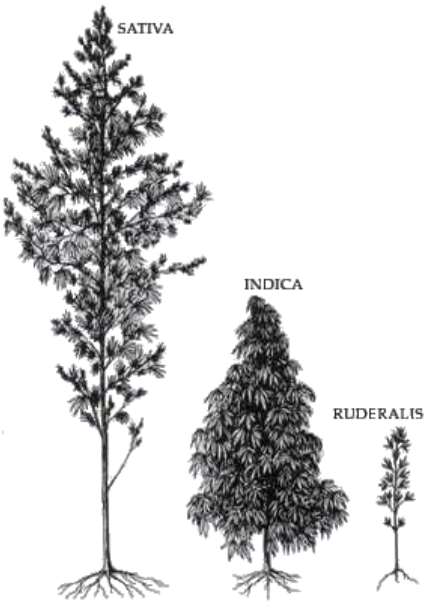
American *Cannabis indica* purchased at a medical cannabis dispensary.



Cannabis indica fluid extract, American Druggists Syndicate, pre-1937.

Difference between *C. indica* and *C. sativa*

Cannabis indica has a higher level of CBD compared to THC, while *Cannabis sativa* has a higher level of THC compared to CBD.[1] Cannabis strains with relatively high CBD:THC ratios are less likely to induce anxiety than vice versa. This may be due to CBD's antagonistic effects at the cannabinoid receptors, compared to THC's partial agonist effect. CBD is also a 5-HT_{1A} receptor agonist, which may also contribute to an anxiolytic effect.[] This likely means the high concentrations of CBD found in *Cannabis indica* mitigate the anxiogenic effect of THC significantly.[] The effects of *sativa* are well known for its cerebral high, hence used daytime as medical cannabis, while *indica* is well known for its sedative effects and preferred night time as medical cannabis.[] The plant *Cannabis sativa* is known to cause more of a "high" by stimulating hunger and by producing a rather more comedic, or energetic feeling. Conversely, the *Cannabis indica* plant is known to cause more of a "stoned" or meditative feeling, possibly because of a higher CBD to THC ratio.[2] The primary effects of *sativas* are on the mind and emotions. These benefits can be

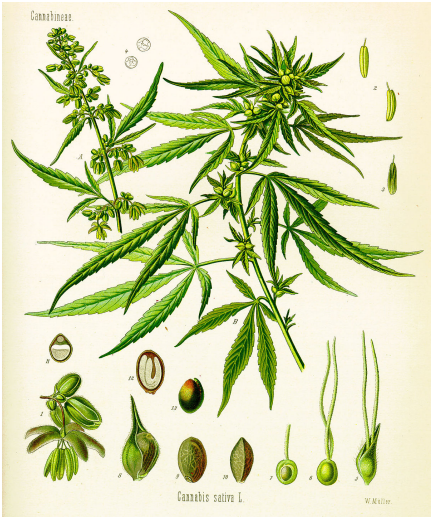


Cannabis sativa, *Cannabis indica*, and *Cannabis ruderalis*

particularly helpful for the psychological aspects of many illnesses, giving people an increased sense of well-being. Due to the stimulating nature of *sativas*, they are generally better for daytime use. Caution should also be taken for people experiencing heightened anxiety or those with mental health conditions.[3] However, this association is contradicted by more recent research which suggests that CBD increases alertness.

Use

Medical cannabis is illegal in most countries. A number of governments, including the U.S. Federal Government, allow treatment with one or more specific low doses of synthetic cannabinoids for one or more disorders. However, public opinion in several areas, including the United States, is swinging in favor of use of medical cannabis, especially for chronically ill patients. The topic is one of great controversy and is being debated more than ever.



Cannabis as illustrated in Köhler's book of medicinal plants from 1897

Studies have shown cannabis does have several well-documented beneficial effects.[][][4][] Among these are: the amelioration of nausea and vomiting, stimulation of hunger in chemotherapy and AIDS patients, lowered intraocular eye pressure (shown to be effective for treating glaucoma), as well as gastrointestinal illness. It also has antibacterial effects[5] and is one of the best known expectorants.[6]

There are several methods for administration of dosage, including vaporizing or smoking dried buds, drinking, or eating extracts, and taking capsules. The comparable efficacy of these methods was the subject of an investigative study[] conducted by the National Institutes of Health.

Synthetic cannabinoids are available as prescription drugs in some countries. Examples are Marinol (The United States and Canada) and Cesamet (Canada, Mexico, the United Kingdom, and the United States).

While utilizing cannabis for recreational purposes is illegal in many parts of the world, many countries are beginning to entertain varying levels of decriminalization for medical usage, including Canada, Austria, Germany, Switzerland, the Netherlands, Czech Republic, Spain, Israel, Italy, Finland, and Portugal. In the United States, federal law outlaws all use of herb parts from Cannabis; States that have approved use of medical cannabis are in conflict with federal law. The United States Supreme Court has ruled in *United States v. Oakland Cannabis Buyers' Coop* and *Gonzales v. Raich* that the federal government has a right to regulate and criminalize cannabis, even for medical purposes. A person can therefore be prosecuted for a cannabis-related crime even if it is legal medical use according to state laws. The US federal government, through the National Institute on Drug Abuse (NIDA), continues to provide medical cannnabis to 4 patients who participated in the Compassionate Investigational New Drug Program.[7] NIDA claims this is done for "compassionate purposes" and the US federal government still maintains that medical marijuana is not an effective or desirable treatment for any medical condition despite significant contrary evidence.

Clinical applications

A 2002 review of medical literature by Franjo Grotenhermen states that medical cannabis has established effects in the treatment of nausea, vomiting, premenstrual syndrome, unintentional weight loss, insomnia, and lack of appetite. Other "relatively well-confirmed" effects were in the treatment of "spasticity, painful conditions, especially neurogenic pain, movement disorders, asthma, [and] glaucoma".[]

"Victoria", the United States' first legal medical marijuana plant grown by The Wo/Men's Alliance for Medical Marijuana.

Preliminary findings indicate that cannabis-based drugs could prove useful in treating adrenal disease, inflammatory bowel disease, migraines, fibromyalgia, and related conditions.[]

Medical cannabis has also been found to relieve certain symptoms of multiple sclerosis[] and spinal cord injuries[][8][9][10][] by exhibiting antispasmodic and muscle-relaxant properties as well as stimulating appetite.

Other studies state that cannabis or cannabinoids may be useful in treating alcohol abuse,[] amyotrophic lateral sclerosis,[11][12] collagen-induced arthritis,[] asthma,[13] atherosclerosis,[14] bipolar disorder,[][15] colorectal cancer,[16] HIV-Associated Sensory Neuropathy,[17] depression,[][18][][19] dystonia,[20] epilepsy,[][21][22] digestive diseases,[23] gliomas,[24][25] hepatitis C,[26] Huntington's disease,[27][28] leukemia,[29] skin tumors,[30] methicillin-resistant *Staphylococcus aureus* (MRSA),[31] Parkinson's disease,[32] pruritus,[33][34] posttraumatic stress disorder (PTSD),[35] psoriasis,[36] sickle-cell disease,[37] sleep apnea,[38] and anorexia nervosa.[39] Controlled research on treating Tourette syndrome with a synthetic version of THC called (Marinol), showed the patients taking the pill had a beneficial response without serious adverse effects;[] other studies have shown that cannabis "has no effects on tics and increases the individuals inner tension".[40] Case reports found that cannabis helped reduce tics, but validation of these results requires longer, controlled studies on larger samples.[41][42]

A study done by Craig Reinarman surveyed people in California who used cannabis found they did so for many reasons. Reported uses were for pain relief, muscle spasms, headaches, anxiety, nausea, vomiting, depression, cramps, panic attacks, diarrhea, and itching. Others used cannabis to improve sleep, relaxation, appetite, concentration or focus, and energy. Some patients used it to prevent medication side effects, anger, involuntary movements, and seizures, while others used it as a substitute for other prescription medications and alcohol.[43]

Recent studies

Safety of cannabis

From The Lancet, "There are no confirmed published cases worldwide of human deaths from cannabis poisoning, and the dose of THC required to produce 50% mortality in rodents is extremely high compared with other commonly used drugs".[44]

According to Associate Professor Emeritus of Psychiatry at Harvard Medical School Lester Grinspoon, "When cannabis regains its place in the US Pharmacopeia, a status it lost after the passage of the Marijuana Tax Act of 1937, it will be seen as one of the safest drugs in that compendium".[]

There are medical reports of occasional infarction, stroke and other cardiovascular side effects.[] Marijuana's cardiovascular effects are not associated with serious health problems for most young, healthy users.[] Researchers have reported in the International Journal of Cardiology, "Marijuana use by older people, particularly those with some degree of coronary artery or cerebrovascular disease, poses greater risks due to the resulting increase in catecholamines, cardiac workload, and carboxyhemoglobin levels, and concurrent episodes of profound postural hypotension. Indeed, marijuana may be a much more common cause of myocardial infarction than is generally

recognized. In day-to-day practice, a history of marijuana use is often not sought by many practitioners, and even when sought, the patient's response is not always truthful. Thus, clinicians should be more vigilant in inquiring about use of marijuana in their patients, particularly among the younger adults who may present with cardiac events in the absence of cardiovascular disease or other obvious risk factors."[45]

A 2012 study published in JAMA and funded by National Institutes of Health looked at a population of over 5,115 American men and women to see whether smoked cannabis has effects on the pulmonary system similar to those from smoking tobacco. The researchers found "Occasional and low cumulative marijuana use was not associated with adverse effects on pulmonary function." Smoking an average of one joint a day for seven years, they found, did not worsen pulmonary health.[46]

Cannabis smoke contains thousands of organic and inorganic chemical compounds. This tar is chemically similar to that found in tobacco smoke or cigars.[47] Over fifty known carcinogens have been identified in cannabis smoke.[48] These include nitrosamines, reactive aldehydes, and polycylic hydrocarbons, including benz[a]pyrene.[49] Marijuana smoke was listed as a cancer agent in California in 2009.[50]

A 2006 study involving 1,212 incident cancer cases and 1,040 cancer-free controls found no causative link to oral, laryngeal, pharyngeal, esophageal or lung cancer when adjusting for several confounding factors including cigarette smoking and alcohol use.[]

Regarding the relative safety of cannabis, former US DEA chief administrative law judge Judge Francis Young said:

> "There is no record in the extensive medical literature describing a proven, documented cannabis-induced fatality....Despite [a] long history of use and the extraordinarily high numbers of social smokers, there are simply no credible medical reports to suggest that consuming marijuana has caused a single death. In practical terms, marijuana cannot induce a lethal response as a result of drug-related toxicity....Marijuana's therapeutic ratio is impossible to quantify because it is so high....Marijuana, in its natural form, is one of the safest therapeutically active substances known to man."[51]Wikipedia:Identifying reliable sources

Pain relief

The effectiveness of cannabis as an analgesic has been the subject of numerous studies. University of Oxford doctors found that the brain on THC showed reduced response to pain, suggesting that the the drug may help patients endure pain. Brain scans showed reduced activity in two centers of the brain where pain is registered: The mid-Anterior cingulate cortex and the right Amygdala. However, cannabis did not block the sensation of pain like morphine-based pain killers.[52] The researchers also found a great degree of variation among individual reports of pain relief.[53]

According to Stuart Silverman, M.D., a rheumatologist at Cedars-Sinai Medical Center, "Historically and anecdotally, marijuana has been used as a painkiller".[54] A Canadian study showed cannabis can reduce "nerve pain" from surgical complications or injuries. The study's twenty-one subjects suffered from chronic pain and patients who smoked cannabis with a 9.4% THC content reported less pain than those patients who smoked the placebo. Improved quality of sleep and reduced anxiety were other reported benefits.[55] Igor Grant, psychiatrist and director of the Center for Medicinal Cannabis Research at the University of California San Diego, has stated, "There is good evidence now that cannabinoids may be either an adjunct or a first-line treatment". Grant explained further that not everyone experienced pain relief, but the percentage of people who did was comparable to those who said that they experienced relief from other medications commonly prescribed for neuropathic pain (the subject of his study), such as antidepressants.[56]

A small-scale UCSF study found that patients with chronic pain may experience greater relief if cannabinoids were added to an opiate-only treatment regime. The findings further suggested that combination therapy could result in reduced opiate dosages.[57] The College of Physicians and Surgeons at Columbia University, U.S. published a study in the *Neuropsychopharmacology* journal in 2013 that is based on research that was conducted with fifteen males and fifteen females who smoked marijuana every day. The study's subjects were exposed to either a placebo, inhaled marijuana, or dronabinol, a pill that contains cannabis' psychoactive ingredient. Participants were monitored to

ensure that they had not smoked in the time period immediately prior to the tests and did not have other drugs (including alcohol) in their systems. The researchers concluded that “Dronabinol administration decreased pain sensitivity and increased pain tolerance that peaked later and lasted longer relative to smoked marijuana”, thereby providing evidence that the pill form was superior to smoked cannabis in terms of pain relief efficacy. However, the Columbia researchers further stated, "A primary caveat of the current findings is that the study population consisted of daily marijuana smokers; this study limitation should be considered when interpreting the findings and placing them within the context of the potential therapeutic feasibility of cannabinoids [for the general population]."[58]

Glaucoma

In glaucoma, cannabis and THC have been shown to reduce intra-ocular pressure (IOP) by an average of 24% in people with normal IOP who have visual-field changes. In studies of healthy adults and glaucoma patients, IOP was reduced by an average of 25% after smoking a cannabis "cigarette" that contained approximately 2% THC—a reduction as good as that observed with most other medications available today, according to a review by the Institute of Medicine.[59]

Medical cannabis in edible form

In a separate study, the use of cannabis and glaucoma was tested and found that the duration of smoked or ingested cannabis or other cannabinoids is very short, averaging 3 to 3.5 hours. Their results showed that for cannabis to be a viable therapy, the patient would have to take in cannabis in some form every 3 hours. They said that for ideal glaucoma treatment it would take two times a day at most for compliance purposes from patients.[60]

Spasticity in multiple sclerosis

A review of six randomized controlled trials of a combination of THC and CBD extracts for the treatment of multiple sclerosis (MS) related muscle spasticity reported, "Although there was variation in the outcome measures reported in these studies, a trend of reduced spasticity in treated patients was noted." The authors postulated that "cannabinoids may provide neuroprotective and anti-inflammatory benefits in MS."[] A small study done on whether or not cannabis could be used to control tremors of MS patients was conducted. The study found that there was no noticeable difference of the tremors in the patients. Although there was no difference in the tremors the patients felt as if their symptoms had lessened and their quality of life had improved. The researchers concluded that the mood enhancing or cognitive effects that cannabis has on the brain could have given the patients the effect that their tremors were getting better.[][61]

Medical cannabis

Alzheimer's disease

Cannabinoids found in medical cannabis prevent or inhibit the progression of Alzheimer's disease.[][]

Research done by the Scripps Research Institute in California shows that the active ingredient in marijuana, THC, prevents the formation of deposits in the brain associated with Alzheimer's disease. THC was found to prevent an enzyme called acetylcholinesterase from accelerating the formation of "Alzheimer plaques" in the brain more effectively than commercially marketed drugs. THC is also more effective at blocking clumps of protein that can inhibit memory and cognition in Alzheimer's patients, as reported in Molecular Pharmaceutics.[] Cannabinoids can also potentially prevent or slow the progression of Alzheimer's disease by reducing tau protein phosphorylation, oxidative stress, and neuroinflammation.[]

A 2012 review from the *Philosophical Transactions of a Royal Society B* suggested that activating the cannabinoid system may trigger an "anti-oxidant cleanse" in the brain by removing damaged cells and improving the efficiency of the mitochrondria. The review found cannabinoids may slow decline in age and disease-related cognitive functioning.[62][63]

Breast cancer

Medical cannabis blocks the spread of breast cancer by downregulating a gene called ID1.[][]

According to a 2007 and a 2010 study at the California Pacific Medical Center Research Institute, cannabidiol (CBD) stops breast cancer from spreading throughout the body by downregulating a gene called ID1.[][] This may provide a non-toxic alternative to chemotherapy while achieving the same results without the painful and unpleasant side effects. The research team says that CBD works by blocking the activity of a gene called ID1, which is believed to be responsible for a process called metastasis, which is the aggressive spread of cancer cells away from the original tumor site.[][] According to findings released by the team in 2012, when the particularly aggressive "triple-negative" cells (which contain high levels of ID1 and account for 15% of breast cancers) were exposed to CBD, they "not only stopped acting 'crazy' but also returned to a healthy normal state". Human trial models are currently in development.[64] Dr Sean McAllister, study co-leader, commented:[65]

> "The preclinical trial data is very strong, and there's no toxicity. There's really a lot of research to move ahead with and to get people excited".

HIV/AIDS

Medical cannabis helps to alleviate pain and to improve quality of life for HIV-positive patients.[][]

Investigators at Columbia University published clinical trial data in 2007 showing that HIV/AIDS patients who inhaled cannabis four times daily experienced substantial increases in food intake with little evidence of discomfort and no impairment of cognitive performance. They concluded that smoked cannabis has a clear medical benefit in HIV-positive patients.[][66] In another study in 2008, researchers at the University of California, San Diego School of Medicine found that marijuana significantly reduces HIV-related neuropathic pain when added to a patient's already-prescribed pain management regimen and may be an "effective option for pain relief" in those whose pain is not controlled with current medications. Mood disturbance, physical disability, and quality of life all improved significantly during study treatment.[] Despite management with opioids and other pain modifying therapies, neuropathic pain continues to reduce the quality of life and daily functioning in HIV-infected individuals. Cannabinoid receptors in the central and peripheral nervous systems have been shown to modulate pain perception. No serious adverse effects were reported, according to the study published by the American Academy of Neurology.[67] A study examining the effectiveness of different drugs for HIV associated neuropathic pain found that smoked Cannabis was one of only three drugs that showed evidence of efficacy.[68]

Brain cancer

THC found in medical cannabis eliminates brain cancer while leaving healthy brain cells intact.[]

A study by Complutense University of Madrid found the chemicals in cannabis promote the death of brain cancer cells by essentially helping them feed upon themselves in a process called autophagy. The research team discovered that cannabinoids such as THC had anticancer effects in mice with human brain cancer cells and in people with brain tumors. When mice with the human brain cancer cells received the THC, the tumor shrank. Using electron microscopes to analyze brain tissue taken both before and after a 26-to 30-day THC treatment regimen, the researchers found that THC eliminated cancer cells while leaving healthy cells intact.[] The patients did not have any toxic effects from the treatment; previous studies of THC for the treatment of cancer have also found the therapy to be well tolerated.[]

Opioid dependence

Medical cannabis is useful in the prevention and treatment of opiate dependence.[][][]

Injections of THC eliminate dependence on opiates in stressed rats, according to a research team at the *Laboratory for Physiopathology of Diseases of the Central Nervous System* (France) in the journal *Neuropsychopharmacology*.[] Deprived of their mothers at birth, rats become hypersensitive to the rewarding effect of morphine and heroin (substances belonging to the opiate family), and rapidly become dependent. When these rats were administered THC, they no longer developed typical morphine-dependent behavior. In the striatum, a region of the brain involved in drug dependence, the production of endogenous enkephalins was restored under THC, whereas it

diminished in rats stressed from birth which had not received THC. Researchers believe the findings could lead to therapeutic alternatives to existing substitution treatments.[]

In humans, drug treatment subjects who use cannabis intermittently are found to be more likely to adhere to treatment for opioid dependence.[] Historically, similar findings were reported by Edward Birch, who, in 1889, reported success in treating opiate and chloral addiction with cannabis.[]

Controlling ALS symptoms

The potential role of cannabis in treating symptoms of ALS (or *Lou Gehrig's Disease*) has been the subject of recent research. A survey was conducted on 131 people suffering from ALS. The survey asked if the subjects had used cannabis in the last 12 months to control some of their symptoms. Of the 131 subjects, 13 had used the drug in some form to control symptoms. The survey found that cannabis was moderately effective in reducing symptoms of appetite loss, depression, pain, spasticity, drooling and weakness, and the longest relief reported was for depression. The pattern of symptom relief was consistent with those reported by people with other conditions, including multiple sclerosis (Amtmann et al. 2004).[]

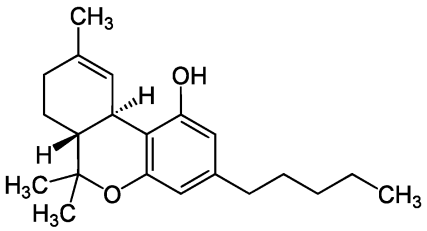
Medical cannabis is moderately effective in reducing symptoms of Amyotrophic lateral sclerosis (ALS) (Lou Gehrig's Disease).[]

Medicinal compounds

Cannabis contains 483 compounds. At least 80 of these are cannabinoids,[69][70] which are the basis for medical and scientific use of cannabis. This presents the research problem of isolating the effect of specific compounds and taking account of the interaction of these compounds.[] Cannabinoids can serve as appetite stimulants, antiemetics, antispasmodics, and have some analgesic effects.[] Six important cannabinoids found in the cannabis plant are tetrahydrocannabinol, tetrahydrocannabinolic acid, cannabidiol, cannabinol, β-caryophyllene, and cannabigerol.

Tetrahydrocannabinol

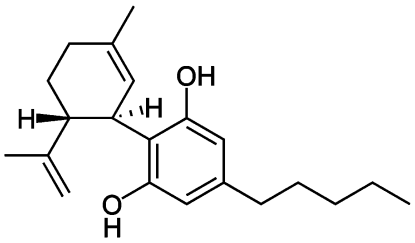
Tetrahydrocannabinol (THC) is the primary compound responsible for the psychoactive effects of cannabis. The compound is a mild analgesic, and cellular research has shown the compound has antioxidant activity.[71] THC is believed to interact with parts of the brain normally controlled by the endogenous cannabinoid neurotransmitter, anandamide.[][] Anandamide is believed to play a role in pain sensation, memory, and sleep.



Chemical structure of tetrahydrocannabinol (THC)

Cannabidiol

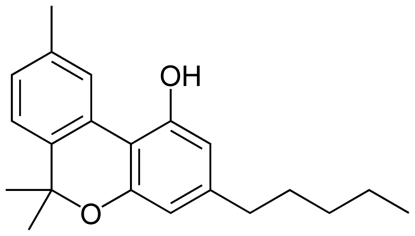
Cannabidiol (CBD) is a major constituent of medical cannabis. CBD represents up to 40% of extracts of medical cannabis.[] Cannabidiol has been shown to relieve convulsion, inflammation, anxiety, cough, congestion and nausea, and it inhibits cancer cell growth.[] Recent studies have shown cannabidiol to be as effective as atypical antipsychotics in treating schizophrenia[72] and psychosis.[73] Because cannabidiol relieves the aforementioned symptoms, cannabis strains with a high amount of CBD may benefit people with multiple sclerosis, frequent anxiety attacks and Tourette syndrome.[][][74]



Cannabidiol has been shown to relieve convulsions, inflammation, anxiety, cough, congestion and nausea, and it inhibits cancer cell growth.[]

Cannabinol

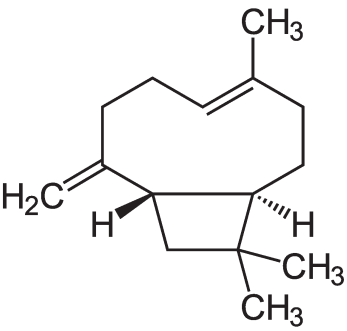
Cannabinol (CBN) is a therapeutic cannabinoid found in *Cannabis sativa* and *Cannabis indica*.[] It is also produced as a metabolite, or a breakdown product, of tetrahydrocannabinol (THC).[] CBN acts as a weak agonist of the CB_1 and CB_2 receptors, with lower affinity in comparison to THC.[][]



Structure of Cannabinol

β-Caryophyllene

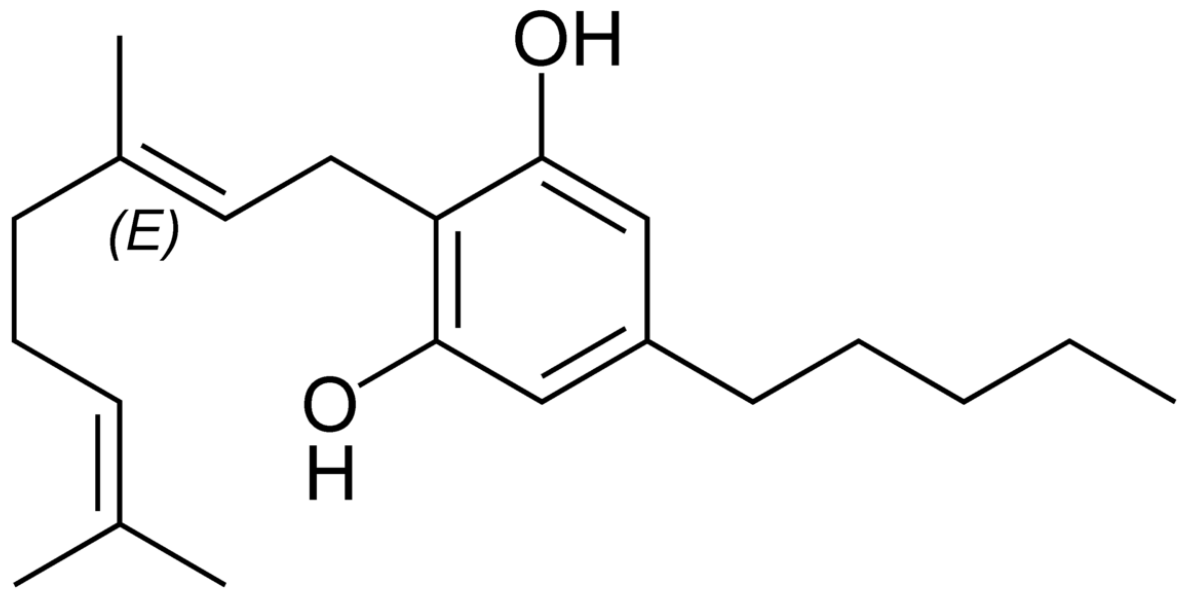
Part of the mechanism by which medical cannabis has been shown to reduce tissue inflammation is via the compound β-caryophyllene.[] A cannabinoid receptor called CB2 plays a vital part in reducing inflammation in humans and other animals.[] β-Caryophyllene has been shown to be a selective activator of the CB2 receptor.[] β-Caryophyllene is especially concentrated in cannabis essential oil, which contains about 12–35% β-caryophyllene.[]



Chemical structure of β-caryophyllene

Cannabigerol

Like cannabidiol, cannabigerol is not psychoactive. Cannabigerol has been shown to relieve intraocular pressure, which may be of benefit in the treatment of glaucoma.[75][76]



Cannabigerol.

Pharmacologic THC and THC derivatives

In the USA, the FDA has approved several cannabinoids for use as medical therapies: dronabinol (Marinol) and nabilone. These medicines are taken orally.

These medications are usually used when first line treatments for nausea and vomiting associated with cancer chemotherapy fail to work. In extremely high doses and in rare cases "psychotomimetic" side effects are possible. The other commonly used antiemetic drugs are not associated with these side effects.

Marinol's manufacturer stated on their website: "The most frequently reported side effects in patients with AIDS during clinical studies involved the central nervous system (CNS). These CNS effects (euphoria, dizziness, or thinking abnormalities, for example) were reported by 33% of patients taking MARINOL".[77][78] Four documented fatalities resulting from Marinol have been reported.[79][80]

Canasol is a cannabis-based medication for glaucoma that relieves intraocular pressure symptoms associated with late-stage glaucoma.

It was created by an ophthalmologist, Dr. Albert Lockhart and Dr. Manley E. West, and began distribution in 1987.[81][82] As of 2003, it was still being distributed in the United Kingdom, several US states, and several Caribbean nations.[83]

It is notable for being one of the first cannabis-containing pharmaceuticals to be developed for the modern pharmaceutical market and being one of the few such pharmaceuticals to have ever been legally marketed in the United States.[82][84]

The prescription drug Sativex, an extract of cannabis administered as a sublingual spray, has been approved in Canada for the adjunctive treatment (use alongside other medicines) of both multiple sclerosis and cancer related pain.[][85] Sativex has also been approved in the United Kingdom, New Zealand, and the Czech Republic, and is expected to gain approval in other European countries.[86][87][88] William Notcutt is one of the chief researchers that has developed Sativex, and he has been working with GW and founder Geoffrey Guy since the company's inception in 1998. Notcutt states that the use of MS as the disease to study "had everything to do with politics."[]

Medication	Approval	Country	Licensed indications	Cost
Nabilone	1985	USA, Canada	Nausea of cancer chemotherapy that has failed to respond adequately to other antiemetics	US$4000.00 for a year's supply (in Canada)[89]
Canasol	1987	USA, Canada, several Caribbean nations	Introcular pressure associated with late-stage Glaucoma	
Marinol	1985	USA Canada (1992)	Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional treatments	US$652 for 30 doses @ 10 mg online[90]
	1992	USA	Anorexia associated with AIDS–related weight loss[91]	
Sativex	1995	Canada	Adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis in adults	C$ 9,351 per year[92]
	1997	Canada	Pain due to cancer	

Criticism

One of the major criticisms of cannabis as medicine is opposition to smoking as a method of consumption. However, smoking is no longer necessary due to the development of healthier methods. Medicinal cannabis patients can use vaporizers, where the essential cannabis compounds are extracted and inhaled. In addition, edible cannabis, which is produced in various baked goods, is also available, and has demonstrated longer lasting effects.

The United States Food and Drug Administration (FDA) issued an advisory[93] against *smoked* medical cannabis stating that, "marijuana has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and has a lack of accepted safety for use under medical supervision." The National Institute on Drug Abuse NIDA state that "Marijuana itself is an unlikely medication candidate for several reasons: (1) it is an unpurified plant containing numerous chemicals with unknown health effects; (2) it is typically consumed by smoking further contributing to potential adverse effects; and (3) its cognitive impairing effects may limit its utility".[94]

The Institute of Medicine, run by the United States National Academy of Sciences, conducted a comprehensive study in 1999 to assess the potential health benefits of cannabis and its constituent cannabinoids. The study concluded that smoking cannabis is not recommended for the treatment of any disease condition, but did conclude that nausea, appetite loss, pain and anxiety can all be mitigated by marijuana. While the study expressed reservations about smoked cannabis due to the health risks associated with smoking, the study team concluded that until another mode of ingestion was perfected that could provide the same relief as smoked cannabis, there was no alternative. In addition, the study pointed out the inherent difficulty in marketing a non-patentable herb. Pharmaceutical companies will probably make less investments in product development if the result is not possible to patent. The Institute of Medicine stated that there is little future in smoked cannabis as a medically approved medication. The report also concluded that for certain patients, such as the terminally ill or those with debilitating symptoms, the long-term risks are not of great concern.[95][96]

Marinol was less effective than the steroid megestrol in helping cancer patients regain lost appetites.[97] A phase III study found no difference in effects of an oral cannabis extract or THC on appetite and quality of life (QOL) in patients with cancer-related anorexia-cachexia syndrome (CACS) to placebo.[98] "Citing the dangers of cannabis and the lack of clinical research supporting its medicinal value" the American Society of Addiction Medicine in March 2011 issued a white paper recommending a halt to using marijuana as a medicine in U.S. states where it has been declared legal.[][]

Mental disorders

A study of 50,000 Swedish soldiers who had smoked at least once were twice as likely to develop schizophrenia as those who had not smoked. The study concluded that either smoking caused a higher rate of schizophrenia, or that those with schizophrenia were more likely to be drawn to cannabis.[99]

A study by Keele University commissioned by the British government found that between 1996 and 2005 there had been significant reductions in the incidence and prevalence of schizophrenia. From 2000 onwards there were also significant reductions in the prevalence of psychoses. The authors say this data is "not consistent with the hypothesis that increasing cannabis use in earlier decades is associated with increasing schizophrenia or psychoses from the mid-1990s onwards".[100]

A 10-year study on 1923 individuals from the general population in Germany, aged 14–24, concluded that cannabis use is a risk factor for the development of incident psychotic disorder symptoms, and the continued use might increase the risk.[101]

However a medical study published in 2009 taken by the Medical Research Council in London, showed there was no significant effect of THC on [11C]-raclopride binding. Thus concluding, recreational cannabis users do not release significant amounts of dopamine from an oral THC dose equivalent to a standard cannabis cigarette. This result challenges current models of striatal dopamine release as the mechanism mediating cannabis as risk factor for schizophrenia.[102]

Lung cancer and chronic obstructive pulmonary disease

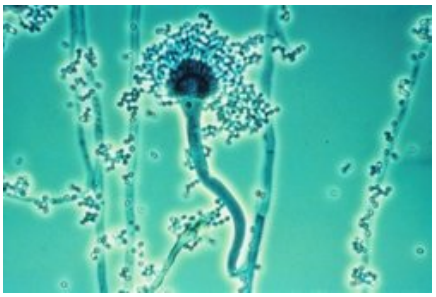
The evidence to date is conflicting as to whether smoking cannabis increases the risk of developing lung cancer or chronic obstructive pulmonary disease (COPD) among people who do not smoke tobacco. In 2006 a study by Hashibe, Morgenstern, Cui, Tashkin, *et al.* suggested that smoking cannabis does not, by itself, increase the risk of lung cancer. Many studies did report a strongly synergistic effect, however, between tobacco use and smoking cannabis such that tobacco smokers who also smoked cannabis dramatically increased their already very high risk of developing lung cancer or chronic obstructive pulmonary disease by as much as 300%. Some of these research results follow below:

- In 2006, Hashibe, Morgenstern, Cui, Tashkin, *et al.* presented the results from a study involving 2,240 subjects that showed non-tobacco users who smoked marijuana did not exhibit an increased incidence of lung cancer or head-and-neck malignancies. These results were supported even among very long-term, very heavy users of marijuana.[] Tashkin, a pulmonologist who has studied cannabis for 30 years, commenting in news reports in the lay media on the results of the study he co-authored, suggested, "It's possible that tetrahydrocannabinol (THC) in cannabis smoke may encourage apoptosis, or programmed cell death, causing cells to die off before they have a chance to undergo malignant transformation". He summarized the results found by his study, saying "We hypothesized that there would be a positive association between cannabis use and lung cancer, and that the association would be more positive with heavier use. What we found instead was no association at all, and even a suggestion of some protective effect."[103][104]
- A case-control study involving 79 cases and 324 controls looked at lung cancer in adults 55 years of age and younger, and found the risk of lung cancer increased 8% (95% confidence interval (CI) 2–15) for each joint-year of cannabis smoking, after adjustment for confounding variables including cigarette smoking, and 7% (95% CI 5–9) for each pack-year of cigarette smoking, after adjustment for confounding variables including cannabis smoking.[105]
- A 2008 study by Hii, Tam, Thompson, and Naughton found that cannabis smoking leads to asymmetrical bullous disease, often in the setting of normal CXR and lung function. In subjects who smoke cannabis, these pathological changes occur at a younger age (approximately 20 years earlier) than in tobacco smokers. However this study involved only 10 patients who also smoked tobacco and had symptoms of the disease prior to the study. There

was no control group in the study.[106] The Journal of the Royal Society of Medicine in 2004 found insufficient evidence for a causative link between cannabis smoke and bullous disease.[107]

- Researchers from the University of British Columbia presented a study at the American Thoracic Society 2007 International Conference showing that smoking cannabis and tobacco together more than tripled the risk of developing COPD over just smoking tobacco alone.Wikipedia:Identifying reliable sources (medicine)[108]Wikipedia:Link rot Similar findings were released in April 2009 by the Vancouver Burden of Obstructive Lung Disease Research Group. The study reported that smoking both tobacco and cannabis synergistically increased the risk of respiratory symptoms and COPD. Smoking only cannabis, however, was not associated with an increased risk of respiratory symptoms of COPD.[109] In a related commentary, pulmonary researcher Donald Tashkin wrote, "...we can be close to concluding that cannabis smoking by itself does not lead to COPD".[110]

Method of consumption



Aspergillus fumigatus

The harm caused by smoking can be minimized or eliminated by the use of a vaporizer[] or ingesting the drug in an edible form. Vaporizers are devices that heat the active constituents to a temperature below the ignition point of the cannabis, so that their vapors can be inhaled. Combustion of plant material is avoided, thus preventing the formation of carcinogens such as polyaromatic hydrocarbons, benzene and carbon monoxide. A pilot study led by Donald Abrams of UC San Francisco showed that vaporizers eliminate the release of irritants and toxic compounds, while delivering equivalent amounts of THC into the bloodstream.[111] According to Matthew Seamon and his co-authors “Vaporizers are the optimal route of administration because they allow for rapid and complete absorption with minimal combustible byproducts, often considered the major health risk associated with smoking tobacco.”[112]

In order to kill microorganisms, especially the molds *A. fumigatus*, *A. flavus* and *A. niger*, Levitz and Diamond suggested baking marijuana at 150 °C (302 °F) for five minutes. They also found that tetrahydrocannabinol (THC) was not degraded by this process.[113]

Pharmaceutical products

- Nabiximols (USAN,[114] trade name **Sativex**) is an aerosolized mist for oral administration intended for the treatment of pain.

Reclassification

A number of medical organizations have endorsed reclassification of marijuana to allow for further study. These include, but are not limited to:

- The American Medical Association[61][][]
- The American College of Physicians – America's second largest physicians group[115]
- Leukemia & Lymphoma Society – America's second largest cancer charity[116]
- American Academy of Family Physicians opposes the use of marijuana except under medical supervision[117]

Other medical organizations recommend a halt to using marijuana as a medicine in U.S.

- The American Society of Addiction Medicine[][]

History

Ancient China and Taiwan

The use of cannabis, at least as fiber, has been shown to go back at least 10,000 years in Taiwan. "Dà má" (Pinyin pronunciation) is the Chinese expression for cannabis, the first character meaning "big" and the second character meaning "hemp."

Cannabis, called *má* 麻 (meaning "hemp; cannabis; numbness") or *dàmá* 大麻 (with "big; great") in Chinese, was used in Taiwan for fiber starting about 10,000 years ago.[118] The botanist Li Hui-Lin wrote that in China, "The use of Cannabis in medicine was probably a very early development. Since ancient humans used hemp seed as food, it was quite natural for them to also discover the medicinal properties of the plant."[119] The oldest Chinese pharmacopeia, the (ca. 100 CE) *Shennong Bencaojing* 神農本草經 ("Shennong's Materia Medica Classic"), describes *dama* "cannabis".

> The flowers when they burst (when the pollen is scattered) are called 麻蕡 [*mafen*] or 麻勃 [*mabo*]. The best time for gathering is the seventh day of the seventh month. The seeds are gathered in the ninth month. The seeds which have entered the soil are injurious to man. It grows in [Taishan] (in [Shandong] ...). The flowers, the fruit (seed) and the leaves are officinal. The leaves and the fruit are said to be poisonous, but not the flowers and the kernels of the seeds.[120]

Emperor Shen-Nung, who was also a pharmacologist, wrote a book on treatment methods in 2737 that included the medical benefits of cannabis. He recommended the substance for many ailments, including constipation, gout, rheumatism, and absent-mindedness.[] Hua Tuo lived many years later, yet he is credited with being the first person known to use cannabis as an anesthetic. He reduced the plant to powder and mixed it with wine for administration.[121] In China, the era of Han Western, the 3rd century the great surgeon Hua Tuo conducts operations under anesthesia using Indian hemp. The Chinese term for anesthesia (麻醉: má zui) is also composed of the ideogram which means hemp, followed by means of intoxication. Elizabeth Wayland Barber says the Chinese evidence "proves a knowledge of the narcotic properties of *Cannabis* at least from the 1st millennium B.C." when *ma* was already used in a secondary meaning of "numbness; senseless." "Such a strong drug, however, suggests that the Chinese pharmacists had now obtained from far to the southwest not THC-bearing *Cannabis sativa* but *Cannabis indica*, so strong it knocks you out cold.[122]

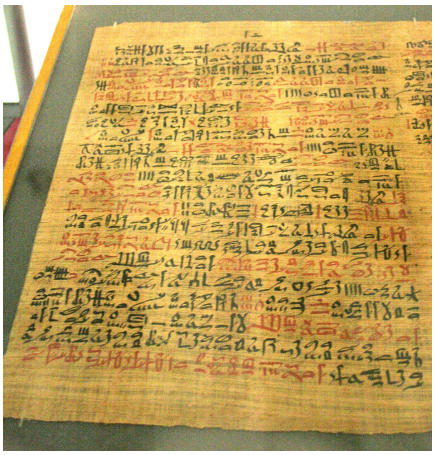
Cannabis is one of the 50 "fundamental" herbs in traditional Chinese medicine,[] and is prescribed to treat diverse indications.

> Every part of the hemp plant is used in medicine; the dried flowers (勃), the achenia (蕡), the seeds (麻仁), the oil (麻油), the leaves, the stalk, the root, and the juice. The flowers are recommended in the 120 different forms of (風 *feng*) disease, in menstrual disorders, and in wounds. The achenia, which are considered to be poisonous, stimulate the nervous system, and if used in excess, will produce hallucinations and staggering gait. They are prescribed in nervous disorders, especially those marked by local anaesthesia. The seeds, by which is meant the white kernels of the achenia, are used for a great variety of affections, and are considered to be tonic, demulcent, alterative, laxative, emmenagogue, diuretic, anthelmintic, and corrective. They are made into a congee by boiling with water, mixed with wine by a particular process, made into pills, and beaten into a paste. A very common mode of exhibition, however, is by simply eating the kernels. It is said that their continued use renders the flesh firm and prevents old age. They are prescribed internally in fluxes, post-partum difficulties, aconite poisoning, vermillion poisoning, constipation, and obstinate vomiting. Externally they are used for eruptions, ulcers, favus, wounds, and falling of the hair. The oil is used for falling hair, sulfur poisoning, and dryness of the throat. The leaves are considered to be poisonous, and the freshly expressed juice is used as an anthelmintic, in scorpion stings, to stop the hair from falling out and to prevent it from

turning gray. They are especially thought to have antiperiodic properties (prevention of regular recurrence of the symptoms of a disease). The stalk, or its bark, is considered to be diuretic, and is used with other drugs in gravel. The juice of the root is used for similar purposes, and is also thought to have a beneficial action in retained placenta and post-partum hemorrhage. An infusion of hemp (for the preparation of which no directions are given) is used as a demulcent drink for quenching thirst and relieving fluxes.[123]

Ancient Egypt

The Ebers Papyrus (ca. 1550 BCE) from Ancient Egypt describes medical cannabis.[] Other ancient Egyptian papyri that mention medical cannabis are the Ramesseum III Papyrus (1700 BC), the Berlin Papyrus (1300 BC) and the Chester Beatty Medical Papyrus VI (1300 BC).[124] The ancient Egyptians even used hemp (cannabis) in suppositories for relieving the pain of hemorrhoids.[125] Around 2,000 B.C., the ancient Egyptians used cannabis to treat sore eyes.[126] The egyptologist Lise Manniche notes the reference to "plant medical cannabis" in several Egyptian texts, one of which dates back to the eighteenth century BCE.[127]



The Ebers Papyrus (ca. 1550 BCE) from Ancient Egypt has a prescription for medical marijuana applied directly for inflammation

Ramesseum III Papyrus (1700 BC)

Papyrus Ramassei III, col. 26:
K.t p<u>h</u>r.t: mɜt.t šmšm.t qnqn, s<u>d</u>r n îɜd.t, î^{c} îr.ty n=s îm dwɜy
Alia praecepta: parsley, hemp and obey, in the dew of rest, wash eyes in that early in the morning

Ancient India

Cannabis was a major component in religious practices in ancient India as well as in medicinal practices. For many centuries, most parts of life in ancient India incorporated cannabis of some form.[] Surviving texts from ancient India confirm that cannabis' psychoactive properties were recognized, and doctors used it for treating a variety of illnesses and ailments. These included insomnia, headaches, a whole host of gastrointestinal disorders, and pain: cannabis was frequently used to relieve the pain of childbirth.[128] One Indian philosopher expressed his views on the nature and uses of bhang (a form of cannabis), which combined religious thought with medical practices. "A guardian lives in the bhang leaf...To see in a dream the leaves, plant, or water of bhang is lucky... A longing for bhang foretells happiness. It cures dysentry and sunstroke, clears hlegm, quickens digestion, sharpens appetite, makes the tongue of the lisper plain, freshens the intellect and gives alertness to the body and gaiety to the mind. Such are the useful and needful ends for which in His goodness the Almighty made bhang.." []

Ancient Greece

The Ancient Greeks used cannabis to dress wounds and sores on their horses.[] In humans, dried leaves of cannabis were used to treat nose bleeds, and cannabis seeds were used to expel tapeworms.[] The most frequently described use of cannabis in humans was to steep green seeds of cannabis in either water or wine, later taking the seeds out and using the warm extract to treat inflammation and pain resulting from obstruction of the ear.[]

In the 5th century BCE Herodotus, a Greek historian, described how the Scythians of the Middle East used cannabis in steam baths. These baths drove the people to a frenzied state. []

The Ancient Greeks used cannabis not only for human medicine, but also in veterinary medicine to dress wounds and sores on their horses.[]

South East Asia

Patani from Asia are primary natural producers of the diuretic, antiemetic, antiepileptic, anti-inflammatory, pain killing and antipyretic properties of *Cannabis sativa*, and used it extensively for 'Kopi Kapuganja' and 'Pecel Ganja', as recreation food, drinks and relaxing medication for centuries.[*citation needed*]

Medieval Islamic world

In the medieval Islamic world, Arabic physicians made use of the diuretic, antiemetic, antiepileptic, anti-inflammatory, Analgesic and antipyretic properties of *Cannabis sativa*, and used it extensively as medication from the 8th to 18th centuries.[129]

Cannabis sativa from *Vienna Dioscurides*, 512 AD

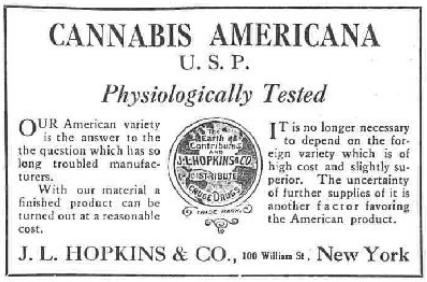
Modern history

Medical cannabis ad from Sweden (1800)

An Irish physician, William Brooke O'Shaughnessy, is credited with introducing the therapeutic use of cannabis to Western medicine. He was Assistant-Surgeon and Professor of Chemistry at the Medical College of Calcutta, and conducted a cannabis experiment in the 1830s, first testing his preparations on animals, then administering them to patients to help treat muscle spasms, stomach cramps or general pain.[]

Cannabis as a medicine became common throughout much of the Western world by the 19th century. It was used as the primary pain reliever until the invention of aspirin.[] Modern medical and scientific inquiry began with doctors like O'Shaughnessy and Moreau de Tours, who used it to treat melancholia and migraines, and as a sleeping aid, analgesic and anticonvulsant. At the local level authorities introduced various laws that required the mixtures that contained cannabis, that was not sold on prescription, must be marked with warning labels under the so-called poison laws.[130]

A Swedish lexicon printed in 1912 describes cannabis drug and cannabis extract as a now with us deserted method for medical treatment.[131]


CANNABIS AMERICANA
U. S. P.
Physiologically Tested

OUR American variety is the answer to the the question which has so long troubled manufacturers. With our material a finished product can be turned out at a reasonable cost.

IT is no longer necessary to depend on the foreign variety which is of high cost and slightly superior. The uncertainty of further supplies of it is another factor favoring the American product.

J. L. HOPKINS & CO., 100 William St., New York

An advertisement for cannabis americana distributed by a pharmacist in New York in 1917.

There were at least 2000 cannabis medicines prior to 1937 with over 280 manufacturers.[132]

Later in the century, researchers investigating methods of detecting cannabis intoxication discovered that smoking the drug reduced intraocular pressure.[133] In 1955 the antibacterial effects were described at the Palacký University of Olomouc. Since 1971 Lumír Ondřej Hanuš was growing cannabis for his scientific research on two large fields in authority of the University. The marijuana extracts were then used at the University hospital as a cure for aphthae and haze.[134] In 1973 physician Tod H. Mikuriya reignited the debate concerning cannabis as medicine when he published "Marijuana Medical Papers". High intraocular pressure causes blindness in glaucoma patients, so he hypothesized that using the drug could prevent blindness in patients. Many Vietnam War veterans also found that the drug prevented muscle spasms caused by spinal injuries suffered in battle.[135] Later medical use focused primarily on its role in preventing the wasting syndromes and chronic loss of appetite associated with chemotherapy and AIDS, along with a variety of rare muscular and skeletal disorders.

In 1964, Dr. Albert Lockhart and Manley West began studying the health effects of traditional cannabis use in Jamaican communities. They discovered that Rastafarians had unusually low glaucoma rates and local fishermen were washing their eyes with cannibis extract in the belief that it would improve their sight. Lockhart and West developed, and in 1987 gained permission to market, the pharmaceutical Canasol: one of the first to cannabis extracts. They continued to work with cannabis throughout the years, developing more pharmaceuticals and eventually receiving the Jamaican Order of Merit for their work.[82]

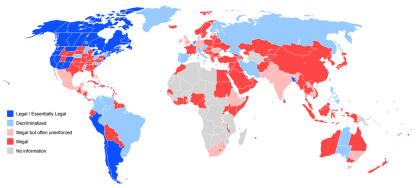
Later, in the 1970s, a synthetic version of THC was produced and approved for use in the United States as the drug Marinol. It was delivered as a capsule, to be swallowed. Patients complained that the violent nausea associated with chemotherapy made swallowing capsules difficult. Further, along with ingested cannabis, capsules are harder to dose-titrate accurately than smoked cannabis because their onset of action is so much slower. Smoking has remained the route of choice for many patients because its onset of action provides almost immediate relief from symptoms and because that fast onset greatly simplifies titration. For these reasons, and because of the difficulties arising from the way cannabinoids are metabolized after being ingested, oral dosing is probably the least satisfactory route for

cannabis administration.[] Relatedly, some studies have indicated that at least some of the beneficial effects that cannabis can provide may derive from synergy among the multiplicity of cannabinoids and other chemicals present in the dried plant material.[136] Such synergy is, by definition, impossible with respect to the use of single-cannabinoid drugs like Marinol.

During the 1970s and 1980s, six U.S. states' health departments performed studies on the use of medical cannabis. These are widely considered some of the most useful and pioneering studies on the subject.[*citation needed*] Voters in eight states showed their support for cannabis prescriptions or recommendations given by physicians between 1996 and 1999, including Alaska, Arizona, California, Colorado, Maine, Michigan, Nevada, Oregon, and Washington, going against policies of the federal government.[137] In May 2001, "The Chronic Cannabis Use in the Compassionate Investigational New Drug Program: An Examination of Benefits and Adverse Effects of Legal Clinical Cannabis" (Russo, Mathre, Byrne et al.) was completed. This three-day examination of major body functions of four of the five living US federal cannabis patients found "mild pulmonary changes" in two patients.[138]

National and international regulations

Medical use of cannabis or preparation containing THC as the active substance is legalized in Canada, Belgium, Austria, Netherlands, UK, Spain, Israel, Finland and some states in the U.S., although it is still illegal under U.S. federal law.



Worldwide laws on cannabis possession for medical purposes.

Cannabis is in Schedule IV of the United Nations´ Single Convention on Narcotic Drugs, making it subject to special restrictions. Article 2 provides for the following, in reference to Schedule IV drugs:[]

> *A Party shall, if in its opinion the prevailing conditions in its country render it the most appropriate means of protecting the public health and welfare, prohibit the production, manufacture, export and import of, trade in, possession or use of any such drug except for amounts which may be necessary for medical and scientific research only, including clinical trials therewith to be conducted under or subject to the direct supervision and control of the Party.*

The convention thus allows countries to outlaw cannabis for all non-research purposes but lets nations choose to allow medical and scientific purposes if they believe total prohibition is not the most appropriate means of protecting health and welfare. The convention requires that states that permit the production or use of medical cannabis must operate a licensing system for all cultivators, manufacturers and distributors and ensure that the total cannabis market of the state shall not exceed that required "for medical and scientific purposes."[]

Africa

Cannabis has been used in Africa since at least the 15th century. Its use was introduced by Arab traders, somehow connected to India. “In Africa, the plant was used for snake bite, to facilitate childbirth, malaria, fever, blood poisoning, anthrax, asthma, and dysentery.” (Zuardi, 2006, 4) Though African governments have tried to limit and stop its use, it still seems to be deeply ingrained, mostly through religious rituals.

Austria

In Austria both Δ^9-THC and pharmaceutical preparations containing Δ^9-THC are listed in annex V of the Narcotics Decree (*Suchtgiftverordnung*).[139] Compendial formulations are manufactured upon prescription according to the German *Neues Rezeptur-Formularium*.[140][]

On 9 July 2008, the Austrian Parliament approved cannabis cultivation for scientific and medical uses.[141] Cannabis cultivation is controlled by the Austrian Agency for Health and Food Safety (*Österreichische Agentur für Gesundheit und Ernährungssicherheit, AGES*).[142]

Canada

Centre compassion de Montréal, au Québec.

In Canada, the regulation on access to cannabis for medical purposes, established by Health Canada in February 2000, defines two categories of patients eligible for access to medical cannabis. BC College of Physicians and Surgeons' recommendation, as well as the CMPA position, is that physicians may prescribe cannabis if they feel comfortable with it. The MMAR forms are a confidential document between Health Canada, the physician and the patient. The information is not shared with the College or with the RCMP. No doctor has ever gone to court or faced prosecution for filling out a form or for prescribing medical cannabis.[] Category 1 covers any symptoms treated within the context of providing compassionate end-of-life care or the symptoms associated with different medical conditions. Category 2 is for applicants who have debilitating symptom(s) of medical condition(s), other than those described in Category 1. The application of eligible patients must be supported by a medical practitioner.[143]

The cannabis distributed by Health Canada is provided under the brand CannaMed by the company Prairie Plant Systems Inc. In 2006, 420 kg of CannaMed cannabis was sold, representing an increase of 80% over the previous year.[144] However, patients complain of the single strain selection as well as low potency, providing a pre-ground product put through a wood chipper (which deteriorates rapidly) as well as gamma irradation and foul taste and smell.[145]

Reception desk at the Kingston Compassion Club Society in Kingston, Ontario

It is also legal for patients approved by Health Canada to grow their own cannabis for personal consumption, and it's possible to obtain a production license as a person designated by a patient. Designated producers were permitted to grow a cannabis supply for only a single patient, however. That regulation and related restrictions on supply were found unconstitutional by the Federal Court of Canada in January 2008. The court found that these regulations did not allow a sufficient legal supply of medical cannabis, and thus forced many patients to purchase their medicine from unauthorized, black market sources. This was the eighth time in the previous ten years that the courts ruled against Health Canada's regulations restricting the supply of the medicine.[] On 14 Dec 2012 the Canadian government announced plans to overhaul its rules regarding medical cannabis [146].

In Canada there are four forms of medical cannabis. The first one is a cannabis extract called Sativex that contains THC and cannabidiol in a spray form. The second is a synthetic or manmade THC called dronabinol marketed as Marinol. The third also a synthetic version of THC called nabilone that is called Cesamet on the markets. The fourth product is the herbal form of cannabis often referred to as marijuana.[147]

Czech Republic

Medical use of cannabis has been legal and regulated in the Czech republic since the 1 April 2013.[148][149]

Germany

In February 2008, seven German patients could legally be treated with medicinal cannabis, distributed by prescription in pharmacies.[150] To regulate therapeutic use, Germany modeled on Dutch neighbor who distributes this way since in 2003 (120 kg in 2008).

In Germany dronabinol was rescheduled in 1994 from annex I to annex II of the Narcotics Law (*Betäubungsmittelgesetz*) in order to ease research; in 1998 dronabinol was rescheduled from annex II to annex III and since then has been available by prescription,[151] whereas Δ^9-THC is still listed in annex I.[152] Manufacturing instructions for dronabinol containing compendial formulations are described in the *Neues Rezeptur-Formularium*.[]

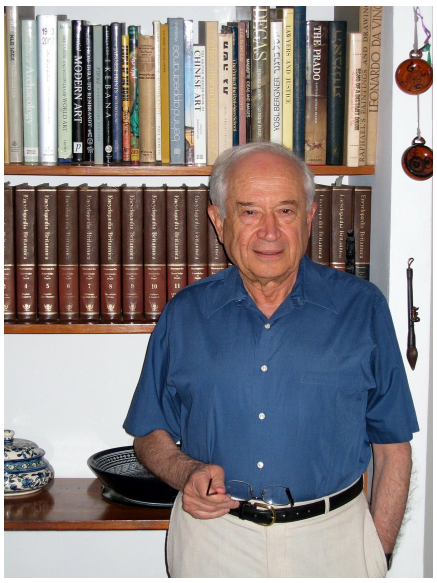
Israel

Marijuana for medical use has been permitted in Israel since the early 1990s for cancer patients and those with pain-related illnesses such as Parkinson's, multiple sclerosis, Crohn's Disease, other chronic pain and post-traumatic stress disorder. Patients can smoke the drug, ingest it in liquid form, or apply it to the skin as a balm. The numbers of patients authorized to use marijuana in Israel in 2012 is about 10,000.[][]

There are eight government-sanctioned cannabis growing operations in Israel, which distribute it for medical purposes to patients who have a prescription from a doctor, via either a company's store, or in a medical center.[]

THC, the psychoactive chemical component in marijuana that causes a high, was first isolated by Israeli scientists Raphael Mechoulam of the Hebrew University in Jerusalem's Center for Research on Pain and Yechiel Gaoni of the Weizmann Institute in 1964.[][]

The Tikkun Olam company has developed a variety of marijuana that is reported to provide the medical benefits of cannabis, but without THC. The cannabis instead contains high quantities of CBD, a substance that is believed to be an anti-inflammatory ingredient, which helps alleviate pain.[][153]



Professor Raphael Mechoulam and Yechiel Gaoni isolated THC from *Cannabis* in 1964 and later discovered anandamide.

Netherlands

Since 2003, the country's pharmacies distribute medicinal cannabis (pharmaceutical form of the natural plant) by prescription, in addition to other drugs containing cannabinoids (dronabinol, Sativex).

Prescription Bedica medical cannabis in the Netherlands

The four therapeutic qualities produced by the company Bedrocan and distributed in the pharmacy are:

- Bedrocan (18% dronabinol / THC. + <1% Cannabidiol / CBD)

- Bedica (14% dronabinol / THC. + <1% Cannabidiol / CBD) granules
- Bediol (11% dronabinol / THC. + <1% Cannabidiol / CBD)
- Bedrobinol (6% dronabinol / THC. + 7.5% Cannabidiol / CBD) granules

Bedrocan

Bediol

Bedrobinol

Spain

In Spain, since the late 1990s and early 2000s, medical cannabis underwent a process of progressive decriminalization and legalisation. The parliament of the region of Catalonia was the first in Spain to have voted unanimously in 2001 legalizing medical marijuana; it was quickly followed by parliaments of Aragon and the Balearic Islands.[*citation needed*] The Spanish Penal Code prohibits the sale of cannabis but it does not prohibit consumption (although consumption on the street is fined). Until early 2000, the Penal Code did not distinguish between therapeutic use of cannabis and recreational use, however, several court decisions show that this distinction is increasingly taken into account by judges. From 2006, the sale of seed is legalized,[*citation needed*] the sale and public consumption remains illegal, and private cultivation and use are permitted to associations.[154][155]

Several studies have been conducted to study the effects of cannabis on patients suffering from diseases like cancer, AIDS, multiple sclerosis, seizures or asthma. This research was conducted by various Spanish agencies at the Universidad Complutense de Madrid headed by Manuel Guzman, the hospital of La Laguna in Tenerife led neurosurgeon Luis González Feria or the University of Barcelona.[*citation needed*]

Several cannabis consumption clubs and user associations have been established throughout Spain. These clubs, the first of which was created in 1991, are non-profit associations who grow cannabis and sell it at cost to its members. The legal status of these clubs is uncertain: in 1997, four members of the first club, the Barcelona Ramón Santos Association of Cannabis Studies, were sentenced to 4 months in prison and a 3000 euro fine, while at about the same time, the court of Bilbao ruled that another club was not in violation of the law. The Andalusian regional government also commissioned a study by criminal law professors on the "Therapeutic use of cannabis and the creation of establishments of acquisition and consumption. The study concluded that such clubs are legal as long as they distribute only to a restricted list of legal adults, provide only the amount of drugs necessary for immediate consumption, and not earn a profit. The Andalusian government never formally accepted these guidelines and the legal situation of the clubs remains insecure. In 2006 and 2007, members of these clubs were acquitted in trial for possession and sale of cannabis and the police were ordered to return seized crops.[155]

United Kingdom

In England and Wales, the use of cannabis medicinally is accepted as a mitigating factor under Sentencing Council guidelines, if it is being cultivated or found in possession of someone.[156] However, in the United Kingdom, possession of small quantities of cannabis does not usually warrant an arrest or court appearance (street cautions or fines are often given out instead). Under UK law, certain cannabinoids are permitted medically,[] but these are strictly controlled with many provisos under the Misuse of Drugs Act 1971 (in the 1985 amendments).

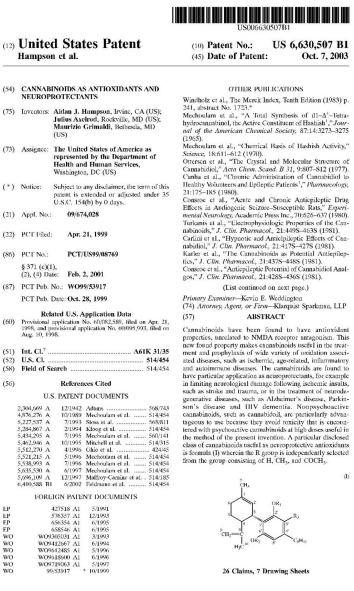
The British Medical Association's official stance is "users of cannabis for medical purposes should be aware of the risks, should enrol for clinical trials, and should talk to their doctors about new alternative treatments; but we do not advise them to stop."[]

United States

In the United States federal level of government, cannabis *per se* has been made criminal by implementation of the Controlled Substances Act which classifies cannabis as a Schedule I drug, the strictest classification on par with heroin, LSD and ecstasy, and the Supreme Court ruled in 2005 that the Commerce Clause of the U.S. Constitution allowed the government to ban the use of cannabis, including medical use. The United States Food and Drug Administration states "marijuana has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and has a lack of accepted safety for use under medical supervision".[][158]

Medical Marijuana Dispensary

Two American (for-profit) companies, Cannabis Science Inc., and Medical Marijuana, Inc., are working towards getting FDA approval for cannabis based medicines (including smoked cannabis). Cannabis Science Inc. wants to have medical cannabis approved by the FDA so anyone, regardless of state, will have access to the medicine.[159] Also, there is one non-profit organization, the Multidisciplinary Association for Psychedelic Studies (MAPS) working towards getting Cannabis approved by the FDA for PTSD.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(12) **United States Patent**
Hampson et al.

(10) **Patent No.: US 6,630,507 B1**
(45) **Date of Patent: Oct. 7, 2003**

(54) **CANNABINOIDS AS ANTIOXIDANTS AND NEUROPROTECTANTS**

(75) Inventors: **Aidan J. Hampson**, Irvine, CA (US); **Julius Axelrod**, Rockville, MD (US); **Maurizio Grimaldi**, Bethesda, MD (US)

(73) Assignee: **The United States of America as represented by the Department of Health and Human Services**, Washington, DC (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(57) **ABSTRACT**

Cannabinoids have been found to have antioxidant properties, unrelated to NMDA receptor antagonism. This new found property makes cannabinoids useful in the treatment and prophylaxis of wide variety of oxidation associated diseases, such as ischemic, age-related, inflammatory and autoimmune diseases. The cannabinoids are found to have particular application as neuroprotectants, for example in limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and HIV dementia. Nonpsychoactive cannabinoids, such as cannabidiol, are particularly advantageous in use because they avoid toxicity that is encountered with psychoactive cannabinoids at high doses useful in the method of the present invention. A particular disclosed class of cannabinoids useful as neuroprotective antioxidants is formula (I) wherein the R group is independently selected from the group consisting of H, CH_3, and $COCH_3$.

26 Claims, 7 Drawing Sheets

The Health and Human Services Division of the Federal government of the United States holds a patent US 6630507 [157] for medical cannabis.

Since the medical marijuana movement began, twenty states and the District of Columbia, starting with California in 1996, have legalized medical cannabis or effectively decriminalized it: Alaska,[] Arizona,[] California,[] Colorado,[] Connecticut,[160][] Delaware,[][161] Hawaii,[] Maine,[] Massachusetts, Michigan,[] Montana,[] Nevada,[] New Jersey,[162] New Mexico,[] Oregon,[] Rhode Island,[] Vermont,[] Virginia,[] Washington;[] and Washington D.C.[163] Maryland allows for reduced or no penalties if cannabis use has a medical basis.[164][165][] Despite its legality in Washington, and Colorado, an employee can still be fired if they test positive on a drug test, despite having a doctor's recommendation.[166] California, Colorado, New Mexico, Maine, Rhode Island, Montana, and Michigan are currently the only states to utilize dispensaries to sell medical cannabis. Connecticut will be the eighth but has yet to issue any licenses. California's medical cannabis industry took in about $2 billion a year and generated $100 million in state sales taxes during 2008[167] with an estimated 2,100 dispensaries, co-operatives, wellness clinics and taxi delivery services in the sector colloquially known as "cannabusiness".[168]

Some individual states such as Oregon choose to issue medical marijuana cards[169] to residents with a doctors recommendation after paying a fee.

On 19 October 2009 the US Deputy Attorney General issued a US Department of Justice memorandum to "All United States Attorneys" providing clarification and guidance to federal prosecutors in US States that have enacted laws authorizing the medical use of marijuana. The document is intended solely as "a guide to the exercise of investigative and prosecutorial discretion and as guidance on resource allocation and federal priorities." The US Deputy Attorney General David W. Ogden provided seven criteria, the application of which acts as a guideline to prosecutors and federal agents to ascertain whether a patient's use, or their caregiver's provision, of medical cannabis

"represents part of a recommended treatment regiment consistent with applicable state law", and recommends against prosecuting patients using medical cannabis products according to state laws. Not applying those criteria, the

Dep. Attorney General Ogden concludes, would likely be "an inefficient use of limited federal resources". The memorandum does not change any laws. Sale of cannabis remains illegal under federal law.[170] The U.S. Food and Drug Administration's position, that marijuana has no accepted value in the treatment of any disease in the United States, has also remained the same.[*citation needed*]

The Health and Human Services Division of the federal government holds a patent US 6630507 [157] for medical cannabis. The patent, "Cannabinoids as antioxidants and neuroprotectants", issued October 2003[] reads:

> "Cannabinoids have been found to have antioxidant properties, unrelated to NMDA receptor antagonism. This new found property makes cannabinoids useful in the treatment and prophylaxis of wide variety of oxidation associated diseases, such as ischemic, age-related, inflammatory and autoimmune diseases. The cannabinoids are found to have particular application as neuroprotectants, for example in limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and HIV dementia... ."[171]

On 17 November 2011, in accordance with 35 U.S.C. 209(c)(1) and 37 CFR part 404.7(a)(1)(i), the National Institutes of Health, Department of Health and Human Services, published in the Federal Register, that it is contemplating the grant of an exclusive patent license to practice the invention embodied in U.S. Patent 6,630,507, entitled "Cannabinoids as antioxidants and neuroprotectants" and PCT Application Serial No. PCT/US99/08769 and foreign equivalents thereof, entitled "Cannabinoids as antioxidants and neuroprotectants" [HHS Ref. No. E-287-1997/2] to KannaLife Sciences Inc., which has offices in New York, U.S. This patent and its foreign counterparts have been assigned to the Government of the United States of America. The prospective exclusive license territory may be worldwide, and the field of use may be limited to: The development and sale of cannabinoid(s) and cannabidiol(s) based therapeutics as antioxidants and neuroprotectants for use and delivery in humans, for the treatment of hepatic encephalopathy, as claimed in the Licensed Patent Rights.[172]

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